Studies in Silicon-Assisted Ring Opening of Cyclopropanes in the Synthesis of Oxacycles, Photochemistry of Thionophosphates, and π-Facial Selectivity of Selected Norbornan-7-ones

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In Partial Fulfillment of the Requirements
for the degree of

DOCTOR OF PHILOSOPHY

by

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to the

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY,
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STATEMENT

I hereby declare that the subject manifested in this thesis, **"Studies in Silicon-Assisted Ring Opening of Cyclopropanes in the Synthesis of Oxacycles, Photochemistry of Thionophosphates, and π-Facial Selectivity of Selected Norbornan-7-ones"**, is the result of research carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India under the supervision of **Professor Veejendra K. Yadav**.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

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Certificate of Course Work

This is to certify that **R. Balamurugan** has satisfactorily completed all the courses required for the Ph.D degree. The courses include:

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CHM 631	Applications of Modern Instrumental Methods
CHM 664	Modern Physical Methods in Chemistry
CHM 612	Frontiers in Organic Chemistry
CHM 681	Basic Biological Chemistry
CHM 800	General Seminar
CHM 801	Graduate Seminar
CHM 799	Postgraduate Research

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...Dedicated to my Father

SYNOPSIS

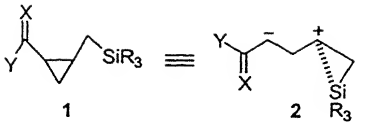
The thesis entitled **"Studies in Silicon-Assisted Ring Opening of Cyclopropanes in the Synthesis of Oxacycles, Photochemistry of Thionophosphates, and π-Facial Selectivity of Selected Norbornan-7-ones"** is divided into three chapters. The title of each chapter and the related summary are given below.

Chapter 1: Silicon-Assisted Ring Opening of Donor-Acceptor Substituted Cyclopropanes. An Expedient Entry to Oxacycles

Cyclopropanes are an important class of building blocks in organic synthesis. The synthetic scope of cyclopropanes is dramatically enhanced when it is vicinally substituted with both donor and acceptor substituents. A donor substituent of much interest has been the trimethylsilylmethyl function. However, the ring opening was always succeeded by the cleavage of the silicon function which limited its scope. We considered placing bulky substituents on silicon which should protect it from the attack of nucleophiles and, thus, avoid its extrusion. The resultant species will, therefore, combine the features of a homo-Michael system and also that of an enolate equivalent as in 2. With this objective in mind, several cyclopropane derivatives carrying different electron attracting groups and bulky trialkylsilylmethyl groups were treated with $TiCl_4$ in CH_2Cl_2. Cyclopropanes bearing two electron-attracting groups underwent facile regioselective ring opening to furnish substituted dihydrofurans in good to excellent yields.

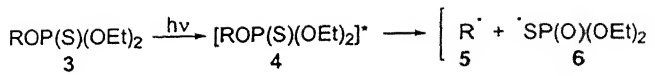
A single phenyl ketone as electron-withdrawing group brought about the ring cleavage smoothly to furnish (3-hydroxy-4-*tert*-butyldiphenylsilyl)butyl phenyl ketone. Since the enolate generated from the phenyl ketone substituted cyclopropane upon treatment with $TiCl_4$ did not cyclize intramolecularly to give the corresponding dihydrofuran derivative, we treated it with electrophiles such as carbonyls since an intermolecular reaction is expected to result in either tetrahydrofuran or tetrahydropyran. In the event, the reaction resulted in the formation of tetrahydrofuran only. The steric bulk of the silyl substituents played a crucial role in both the dihydrofuran and tetrahydrofuran formations. Substrates bearing less bulky silyl substituents resulted in the formation of different products with the extrusion of the silicon moiety.

As an extension, we considered generating a carbocationic center adjacent to the cyclopropane ring from the corresponding cyclopropyl carbinol. The intramolecular trapping of the ring-opened silicon-stabilized β-carbocation with a tethered hydroxyl function is expected to result in γ-methylene oxacycles. In this context, cyclopropyl biscarbinols containing vicinal *tert*-butyldiphenylsilylmethyl group were treated with *p*-TSA in THF to obtain 3-methylene-5-(*tert*-butyldiphenylsilylmethyl)tetrahydrofuran in good yield. This method was applied to the synthesis of 6- and 7-membered γ-methylene oxacycles as well. In further exploitation we synthesized α-ethylidene-γ-lactones and β-ethylidene-δ-lactones from cyclopropane derivatives bearing one hydroxyl and one-ester functions.



Chapter 2: Photochemistry of Thionophosphates

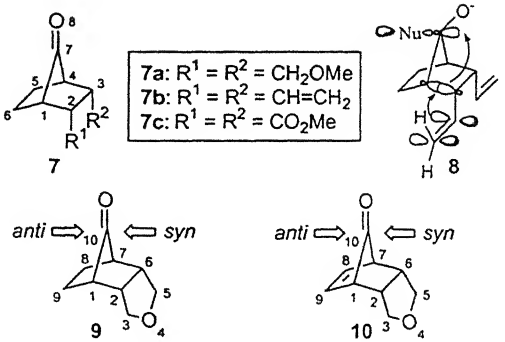
The photochemistry of aryl, arylmethyl, and naphthyl phosphates, $ROP(O)(OEt)_2$, has been shown to involve ionic intermediates. In this chapter, we describe the photochemistry of thionophosphates, $ROP(S)(OEt)_2$, **3**, which proceeds predominantly through a non-chain radical pathway. Simple photoirradiation of thionophosphates derived from benzyl and vinylogously benzyl alcohols with a Hanovia medium-pressure mercury lamp in a quartz vessel led to the formation of the corresponding thiolophosphates, $RSP(O)(OEt)_2$. Thionophosphates derived from non benzylic alcohols did not react. This suggests the necessity of an aromatic chromophore at the carbinol carbon for a meaningful reaction to take place. The generation of radical intermediates **5** and **6** has been advantageously utilized in the benzylation of solvents such as *i*-PrOH, THF and toluene and allylic benzylation of olefins. When the irradiation of the thionophosphates was carried out in the presence of allyl bromides, only the sulfur-centered radical **6** and not the benzyl radical **5** added to the allyl bromide. The involvement of radical intermediates and non-chain radical pathways were established by a series of specially designed experiments. Attempts at the cleavage of cyclopropane ring were also made to give further insights of the mechanism.



Chapter 3: Validity of the Rigid Conformer Concept in the Face Selection of some Norbornan-7-ones towards Nucleophilic additions

The factors governing the discrimination of the two faces of a trigonal carbon towards nucleophilic additions have been a subject of intense debate. Norbornan-7-ones, that are rigid and devoid of significant geometrical distortion around the carbonyl function, offer an opportunity to evaluate the role of different factors. The *anti*-selectivities of substrates **7a** and **7b** have been attributed to through space donations from these substituents in rigid conformers such as **8** for **7b**. We have employed the cation complexation model to evaluate its applicability to these systems and also to test the merits of the rigid conformer concept. While the rigid conformer concept for **7b** is valid in explaining its *anti*-selectivity, it is not for **7a**. In **7a**, it is rather the electron-donating interaction of one of the two methylene C-H bonds with σ^*_{C1-C2} that plays the key role in promoting the *anti*-pyramidalization. To support the above arguments, nucleophilic reactions were carried out on substrates **9** and **10** wherein the ring oxygen is held in a rigid conformation. There was a strong dependence of the selectivity on the specific hydride used and the reaction solvent employed. The species **10** exhibited *anti*-selectivity throughout. Lewis acids promoted *anti*-addition to both **9** and **10**. The experimental

selectivities of both **9** and **10** are controlled by the antiperiplanar effects that render $\sigma_{C1\text{-}C2}$ and $\sigma_{C6\text{-}C7}$ more electron-rich than $\sigma_{C1\text{-}C9}$ and $\sigma_{C7\text{-}C8}$ by electron-donation from a C-H bond on C3 and C5.



7 8 9 10

Table of Contents

List of Abbreviations used

Acc	Acceptor
AM1	Austin model 1
Anal. Calcd.	Analytically calculated
app	Anti periplanar
aq	Aqueous
CAN	Ceric ammonium nitrate
cat.	Catalytic
m-CPBA	*m*-Chloroperbenzoic acid
CNDO	Complete neglect of differential overlap
DIBAL-H	Diisobutylaluminium hydride
DMD	Dimethyl dioxirane
DME	Dimethoxyethane
DMSO	Dimethyl sulfoxide
DNP	2,4-Dinitrophenylhydrazine
Do	Donor
EtOAc	Ethyl acetate
IR	Infrared
ISC	Intersystem crossing
LAH	Lithium aluminium hydride
lp	Less polar (TLC)
MOPAC	Molecular orbital package
mp	More polar (TLC)
NBO	Natural bond order

NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
RCM	Ring closing metathesis
rt	Room temperature
L-Selectride	Lithium tri-*sec*-butylborohydride
ST	Singlet to Triplet Conversion
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TS	Transition state
p-TSA	*p*-Toluenesulfonic acid
p-TSCl	*p*-Toluenesulfonyl chloride

Chapter 1

Silicon-Assisted Ring Opening of Donor-Acceptor Substituted Cyclopropanes. An Expedient Entry to Oxacycles

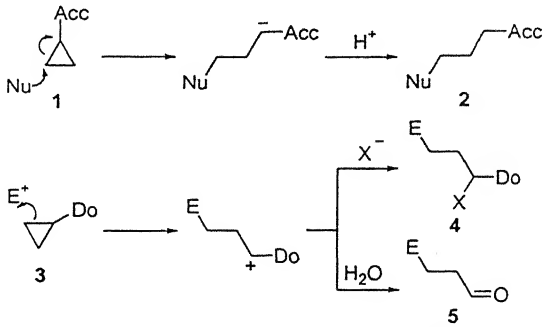
1.1 Introduction

Cyclopropanes are an important class of building blocks in organic synthesis.[1] It was only after the early 70s that their importance in the synthesis of a variety of useful molecular skeletons was recognized and, since then, the exploration of their synthetic utilities has been an active area of research. Owing to the inherent ring strain, cyclopropanes possess good reactivity.[1b] Such a reactivity is well established from the nature of bonding and energetics in cyclopropanes. The sp^3 hybrid orbitals are out of alignment by approximately 22° from the vertices of the triangle formed by the three ring carbons of the cyclopropane. These 'bent' bonds have 20% less orbital overlap than the corresponding bond in ethane. In addition to this, poor orbital overlap, angular (Bayer) strain, and torsional (Pitzer) strain due to the eclipsing carbon-hydrogen bonds also contribute much to their reactivity. The chemical reactivity of cyclopropane is closely related to that of an olefin. Like the olefinic double bond, the σ bond of cyclopropane ring interacts with the neighboring π-electron systems. Both the systems undergo similar reactions such as addition of acids,

halogens, and ozone, catalytic hydrogenation, cycloadditions, and formation of metal complexes. Thus, cyclopropanes are generally considered as equivalent of a double bond but with one extra carbon to their advantage.

1.1.1 General reactivity of substituted cyclopropanes

The reactivity pattern of a cyclopropane ring is highly influenced by its substituents, in general, and their nature, in particular.[1c] Different substituents force the cyclopropane ring to opt entirely different reaction pathways. For example, an electron deficient center enlarges the three-membered ring into a four-membered ring. A vinylic substituent brings about a C_3-to-C_5 ring enlargement.[1a] The regio- and the stereoselectivities of the reactions of cyclopropanes are also heavily dependent on the nature of the substituents. Thus, substituents are fine tuner of reactivity and selectivity in the reactions of cyclopropanes. Cyclopropane ring could be made to react selectively with either an electrophile or a nucleophile by properly choosing the substituents on it. An acceptor cyclopropane such as **1** acts as a homo Michael system and it is attacked by nucleophiles to result in **2**. Conversely, a donor cyclopropane such as **3** is attacked by electrophiles to give either **4** or **5**, depending upon the nature of the donor function (Scheme 1). Thus donor-substituted cyclopropanes are regarded as homo-enolate equivalents.



Scheme 1. Ring opening of donor and acceptor substituted cyclopropanes

The synthetic scope of cyclopropanes is dramatically enhanced when it is substituted with both donor and acceptor substituents as it is now adorned with what may be considered double activation. The advantage of such donor-acceptor substituted cyclopropanes is two fold. First, the cyclopropane ring cleavage occurs under relatively milder conditions and, second, it results in products with at least two new functional groups. Two modes are possible for two such substituents. The geminally substituted donor-acceptor cyclopropane **6** has limited scope as it undergoes mainly C_3-to-C_4 and C_3-to-C_5 ring expansions.[1d] The vicinally substituted donor-acceptor substituted cyclopropane **7** is a potential synthetic intermediate in organic synthesis as it couples both the homo Michael and homo enolate characters as depicted in **8** (Figure 1) and, thus, it can add to both nucleophiles and electrophiles.

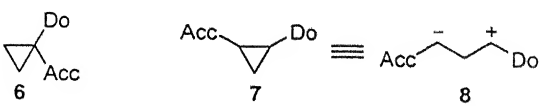


Figure 1

The donor-acceptor cyclopropanes bearing alkoxy and silyloxy groups as the donor substituents have been studied extensively. They find decent application in the synthesis of a variety of carbocycles and heterocycles. Alkylthio, arylthio, and amino substituents are amongst the less studied donor substituents.

1.1.2 Silicon assisted ring opening of cyclopropanes

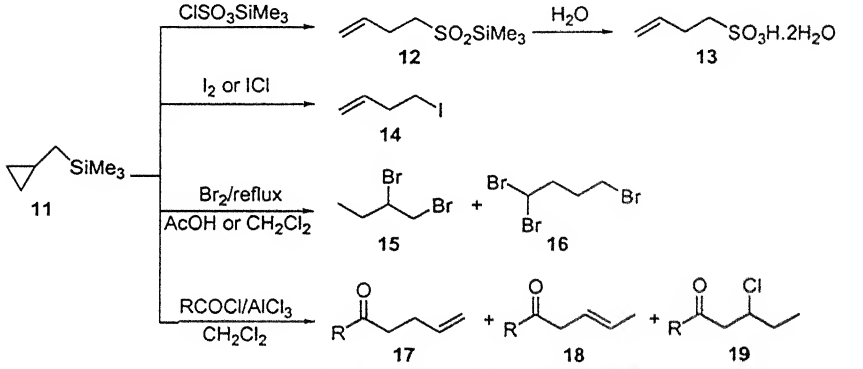
Another interesting donor substituent of much interest is the trimethylsilylmethyl function mainly because of certain unique properties associated with the silicon atom such as (i) its relatively lower electronegativity than carbon, and (ii) its ability to expand its valency to enhance the reactivity under specific circumstances. These properties of silicon enable it to stabilize a positive charge on the β carbon, a subject for much mechanistic, synthetic, and theoretical investigations.[2] Its magnitude has been calculated as 38 kcal mol^{-1}. The mode of stabilization of a β-carbocation could be through either hyperconjugation without significant movement in the transition state as in **9** or the internal neighboring group participation to form the silaranium cation **10** in which the pentavalency of silicon is allowed by its *d* orbitals (Figure 2).

9 **10**

Figure 2. Possible modes of stabilization of a β-carbocation by silicon

1.1.2.1 Donor substituted cyclopropanes

Dubois *et al.* have studied extensively the ring opening of cyclopropanes assisted by a trimethylsilylmethyl substituent.[3] In all the cases, the silicon moiety is lost and the reaction generally resulted in substituted olefins. In their initial studies, they sulfonated different (cyclopropylmethyl)trimethylsilanes such as **11** with trimethylsilylchlorosulfonate to obtain trimethylsilyl mono- and disulfonates which, on further treatment with water, gave new sulfonic acids (Scheme 2).[3a]

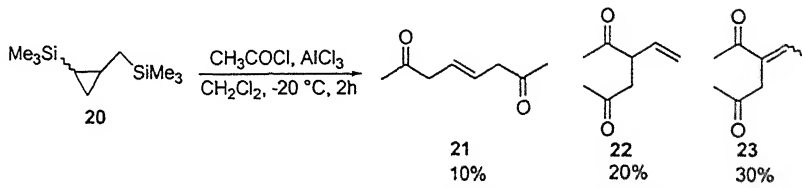


Scheme 2. Electrophilic ring opening of **11**

Electrophilic attack of I_2 and ICl on (cyclopropylmethyl)trimethylsilane resulted in ring-cleavage to give 4-iodo-1-butene **14**.[3b] However, Br_2, being more reactive towards double bonds, added further to give 1,2-dibromobutane **15** and 1,1,4-tribromobutane **16**.

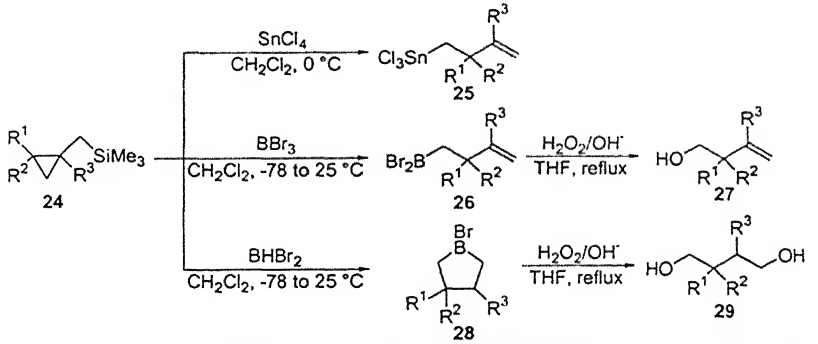
The $AlCl_3$-promoted acylation of **11** with RCOCl gave a mixture of three products **17**, **18**, and **19**. With almost all the acyl chlorides studied except the α,β-unsaturated acyl halides, the β,γ-

unsaturated ketones **18** were the major product.[3c] Thus, it constitutes a simple method for the synthesis of β,γ-unsaturated ketones. Both the *cis*- and *trans*-isomers of 1-trimethylsilyl-2-(trimethylsilylmethyl)cyclopropane **20** did not undergo regioselective ring opening although it had two activating donor substituents to facilitate the same.[3d] Rather, it gave a mixture of products, **21-23**, under mild conditions (Scheme 3).



Scheme 3. $AlCl_3$- promoted acetylation of **20**

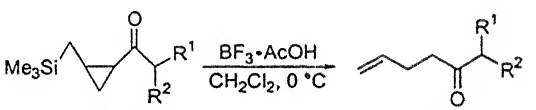
Ryu *et al.* have studied the electrophilic ring opening of a variety of substituted (cyclopropylmethyl)trimethylsilanes **24** with $SnCl_4$, BBr_3, and $BHBr_2$.[4] $SnCl_4$-assisted ring cleavage was highly regioselective as it resulted in the formation of homoallylic trichlorostannanes, **25**.[4a] Likewise, the electrophilic attacks involving BBr_3 and $BHBr_2$ were also highly site-selective and took place at the least substituted cyclopropane ring carbon.[4b] Homoallylboranes **26** and boracyclopentanes **28** thus obtained from the respective reactions of BBr_3 and $BHBr_2$ were easily converted into homoallylic alcohols **27** and 1,4-diols **29**, respectively, by oxidation with alkaline H_2O_2 (Scheme 4).



Scheme 4. Electrophilic ring opening of **24** with $SnCl_4$, BBr_3, and $BHBr_2$

1.1.2.2 Donor-acceptor substituted cyclopropanes

Only a few methods are available for the ring opening of donor-acceptor substituted cyclopropanes possessing trimethylsilylmethyl group as the donor function. Vicinally donor-acceptor substituted cyclopropyl ketones **30** underwent smooth ring opening assisted by the trimethylsilyl group under Lewis acidic conditions (Scheme 5).[5]

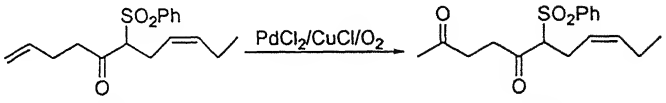


30a-30g → **31a-31g**, 67-97%

a: R^1 = H, R^2 = SO_2Ph
b: R^1 = *n*-C_5H_{11}, R^2 = SO_2Ph
c: R^1 = *n*-C_5H_{11}, R^2 = H
d: R^1 = H, R^2 = SO_2Me
e: R^1 = Me, R^2 = SO_2Ph
f: R^1 = ph, R^2 = H
g: R^1 = H_2C, CH_3, R^2 = SO_2Ph

Scheme 5. BF_3· AcOH-assisted ring opening of donor-acceptor substituted cyclopropanes **30a-30g**

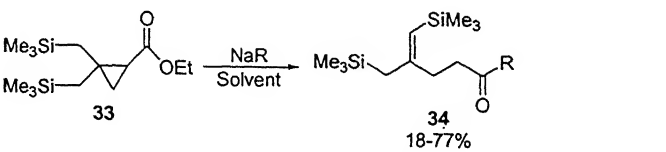
This method was applied to the formal synthesis of *cis*-jasmone. Palladium-catalyzed oxidation of the terminal olefin in **31g** furnished the diketone **32**, a key intermediate for the synthesis of *cis*-jasmone (Scheme 6). Similarly, **31c** was converted into its corresponding diketone, a key precursor for the synthesis of dihydrojasmone.



31g **32** 77%

Scheme 6

Nucleophilic displacement on ester function of **33** with the sodium salt of a sulfone or a sulfoxide under basic conditions in solvents such as DME/DMSO or THF or THF/DMSO showed unusual ring opening to afford ethyl-2,2-bis(trimethylsilyl)propenes **34** (Scheme 7).[6] The rapid ring opening occurred presumably from the corresponding acylated derivative of **33**. This is attributed to the severe destabilizing steric strain between the acyl substituent and the trimethylsilylmethyl group *syn* to it.



33 **34** 18-77%

34a: R = CH_2SO_2Ph
34b: R = CH_2SO_2Me
34c: R = $CH(SO_2Ph)CH_2CHCHCH_2CH_3$

Scheme 7

Fluoride ion-promoted cleavage of the methyl (2-trimethylsilylmethyl)cyclopropylcarboxylate has been studied by

Reissig and co-workers.[7] The intermediate enolate of methyl 4-pentenoate formed upon ring opening with the elimination of trimethylsilyl group, gave methyl 4-pentenoate on quenching with water. Surprisingly, no α-methylated methyl 4-pentenoate was formed in the reaction when the reaction was quenched with methyl iodide.

1-Acylimidazole **35** serves as a 1,2-dipole as shown in **36** (Figure 3) and it undergoes cycloadditions with diethyl maleate and ethyl 2-ethoxycarbonyl-2,4-hexadienoate to give substituted cyclobutanones **37** and **38**, respectively, upon ring opening with CsF (Scheme 8).[8] The success of this reaction is probably due to the electrophilic 1-acylimidazole moiety which assists the ring opening and the leaving ablility of imidazole group to generate a positive center on the carbonyl carbon.

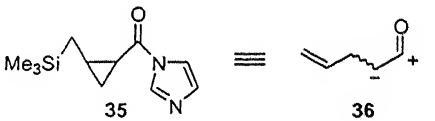
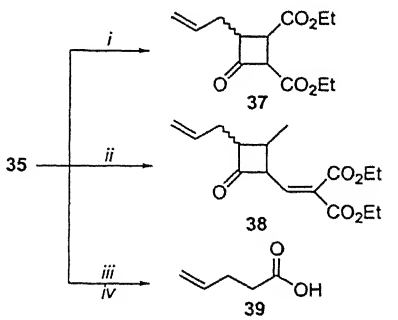


Figure 3



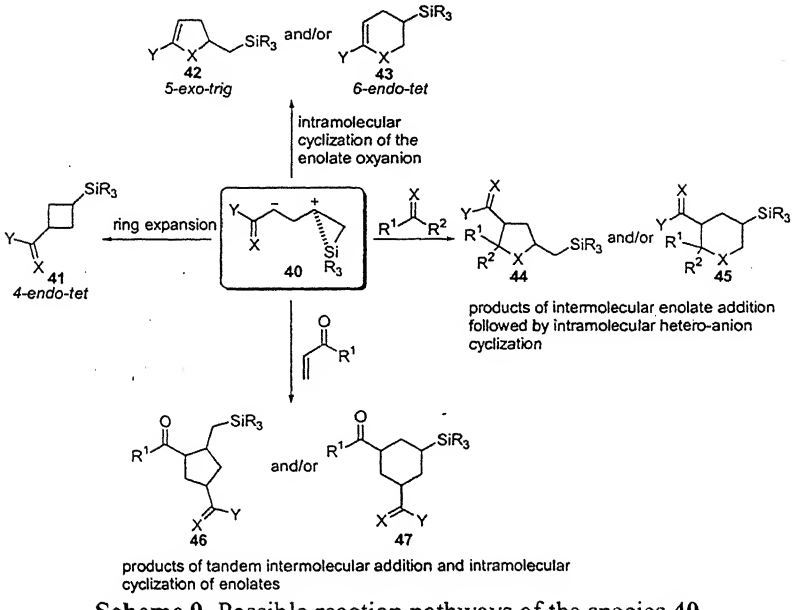
Reagents and conditions: *i*, $EtO_2CCH{=}CHCO_2Et$ (6 equiv), CsF (2 equiv), MeCN, reflux, 6 h, 65%; *ii*, $MeCH{=}CHCH{=}CHC(CO_2Et)_2$ (5 equiv), $H_2C{=}C(CO_2Et)_2$ (1 equiv), CsF (2 equiv), MeCN, reflux, 5 h, 58%; *iii*, $BF_3{\cdot}OEt_2$ (1 equiv), CH_2Cl_2, rt, 24 h; *iv*, H_2O, 83% in two steps.

Scheme 8. Cycloaddition of dienophiles with the species **36** generated from **35**

1.2 Present Work:

1.2.1 Objectives:

In all the cases except the alkylative ring opening of **33** described in the preceeding sections, the carbon-silicon bond is cleaved to effect the ring opening. Furthermore, in **33**, the ring opening occurred without the extrusion of the silicon function only because of the steric encumbrance caused by the bulky acyl substituent and the trimethylsilylmethyl group *syn* to it. The restricted scope of these cyclopropane ring openings, as evident from the limited literature information, is due to the extrusion of the important silicon function. Hence, methods are required to bring about the ring opening without the extrusion of the silicon function. In doing so, the resulting ring opened species will have the features of a homo Michael system and also that of an enolate equivalent as in **40**. The species **40** may be expected to undergo either an intramolecular cyclization through the enolate carbon to give a cyclobutane derivative **41** that involves 1,2-silyl migration or an intramolecular cyclization of the enolate oxyanion on the siliranium ion to give dihydrofuran **42** or dihydropyran **43**, or both. The reaction of the dipole **40** with electrophiles such as aldehydes, ketones, and Michael acceptors is expected to result in the cycloadducts **44-47**. The reaction involves an initial intermolecular attack of the enolate on the electrophile which is followed by an intramolecular ring closure (Scheme 9).



Scheme 9. Possible reaction pathways of the species **40**

The best way to achieve the above objective could be the placement of bulky substituents on silicon as these would prevent the silicon from attacked by nucleophiles. This has good literature precedents in allylsilane chemistry. When one or more of the methyl groups in allyltrimethylsilane are replaced by bulky groups such as isopropyl, phenyl, and *tert*-butyl, it behaves as either a 1,3-dipole with 1,2-migration of silicon or a 1,2-dipole with no migration of silicon (Figure 4).

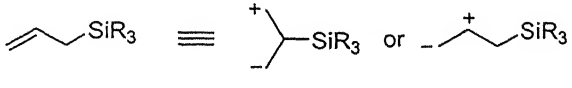
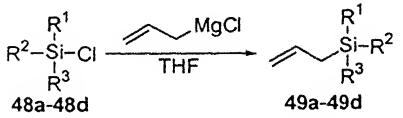


Figure 4

This idea finds a good application in the synthesis of substituted cyclobutanes, cyclopentanes, tetrahydrofurans, tetrahydropyrrolidines, and oxetanes.[9] An added advantage of having a silyl substituent in the product is that it serves as a masked hydroxyl function for further synthetic manipulations when at least one of its substituents is a phenyl group.[10]

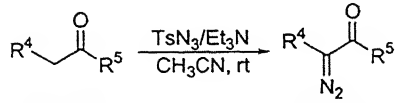
1.2.2 Starting Materials

With the above objective in mind, we prepared the required cyclopropane derivatives carrying different electron attracting groups and bulky trialkylsilylmethyl groups following the Schemes 10 and 11. Allylsilanes, **49a-49d**, carrying different silyl substituents were prepared by allowing an allyl Grignard to react with the corresponding trialkylsilyl chlorides, **48a-48d**, following a literature protocol (Scheme 10).[11] The diazo compounds **51a-51j** used for the preparation of **52-64** were prepared by standard methods as given in the Scheme 10.[12] The allylsilanes **48a-48d** were subjected to standard rhodium-catalyzed carbene insertion reaction with the corresponding diazo compounds to obtain the required cyclopropane derivatives **52-64** (Scheme 11).



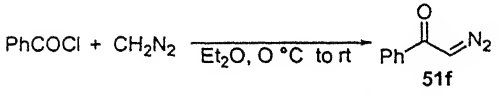
48a-48d **49a-49d**

a: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$
b: $R^1 = R^2 = R^3 = i\text{-Pr}$
c: $R^1 = R^2 = Me$, $R^3 = Ph$
d: $R^1 = R^2 = R^3 = Me$

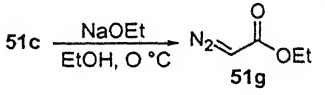


50a-50e **51a-51e**

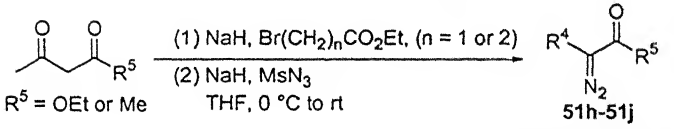
51a: $R^4 = CO_2Me$, $R^5 = OMe$
51b: $R^4 = COMe$, $R^5 = Me$
51c: $R^4 = CO_2Et$, $R^5 = Me$
51d: $R^4 = SO_2Ph$, $R^5 = OEt$
51e: $R^4\text{-}R^5 = COCH_2CH_2CH_2$



51f



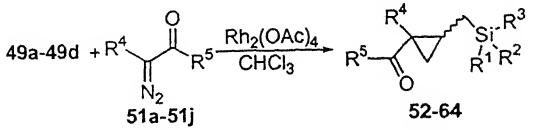
51g



51h-51j

51h: $R^4 = CH_2CO_2Et$, $R^5 = OEt$
51i : $R^4 = CH_2CH_2CO_2Et$, $R^5 = OEt$
51j : $R^4 = CH_2CO_2Et$, $R^5 = Me$

Scheme 10. Preparation of allylsilanes **49a-49d** and diazo compounds **51a-51j**



52: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$, $R^4 = CO_2Me$, $R^5 = OMe$
53: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$, $R^4 = COMe$, $R^5 = Me$
54: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$, $R^4 = CO_2Et$, $R^5 = Me$
55: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$, $R^4 = SO_2Ph$, $R^5 = OEt$
56: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$, $R^4 = H$, $R^5 = Ph$
57: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$, $R^4 = H$, $R^5 = OEt$
58: $R^1 = R^2 = R^3 = i\text{-Pr}$, $R^4 = CO_2Me$, $R^5 = OMe$
59: $R^1 = R^2 = Me$, $R^3 = Ph$, $R^4 = CO_2Me$, $R^5 = OMe$
60: $R^1 = R^2 = Me$, $R^3 = Ph$, $R^4 = H$, $R^5 = Ph$
61: $R^1 = R^2 = R^3 = Me$, $R^4 = H$, $R^5 = Ph$
62: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$, $R^4 = CH_2CO_2Et$, $R^5 = OEt$
63: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$, $R^4 = CH_2CH_2CO_2Et$, $R^5 = OEt$
64: $R^1 = R^2 = Ph$, $R^3 = t\text{-Bu}$, $R^4 = CH_2CO_2Et$, $R^5 = Me$

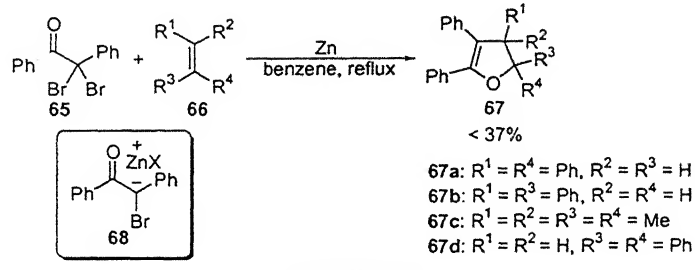
Scheme 11. Preparation of cyclopropane derivatives **52-64**

1.2.3 Synthesis of Dihydrofurans

Cyclic ethers are often found in many naturally occurring compounds and, furthermore, are useful synthetic intermediates.[13] Hence, methods directing at their syntheses are in good demand. Only a few methods are known for the synthesis of dihydrofurans. These are discussed below.

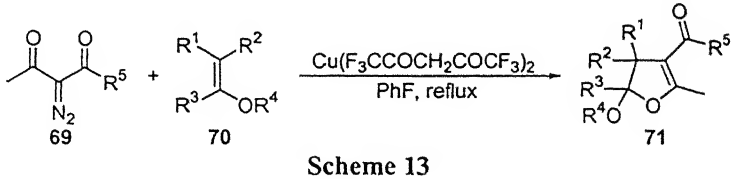
Scott and Cotton trapped the ketocarbenoid intermediate formed from α,α-dibromodeoxybenzoin on reflux with zinc dust in benzene with different olefins such as *cis*- and *trans*-stilbene, tetramethylethylene, and 1,1-diphenylethylene to get the corresponding dihydrofuran derivative (Scheme 12).[14] The reactions generally required long reaction times and the yields were poor. Experiments supported the involvement of the bromoenolate **68** that was formed by α-elimination similar to the first step in Reformatsky reaction.

However, no comments were made in regard to the stereospecificity, both the *cis*- and *trans*-stilbenes gave the *trans*-isomer only.



Scheme 12

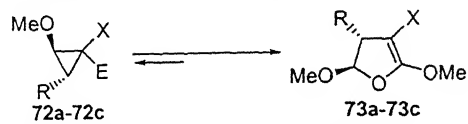
Alonso *et al.* prepared a series of 4-(alkoxycarbonyl)- and 4-acyl-2,3-dihydrofurans **71** in moderate to good yields by a copper chelate-catalyzed thermolysis of alkyl-2-diazo-3-oxobutyrate and 3-diazo-2,4-pentanedione, **69**, in the presence of several vinyl ethers **70** carrying different substituents (Scheme 13).[15] These cycloadditions are highly regioselective as the enolate oxyanion forms the bond preferentially with the vinylic carbon attached to the alkoxy function. The authors have proposed a stepwise addition of the ketocarbenoid to the olefin.



Scheme 13

Electrophilic cyclopropanes, **72a-72c**, undergo smooth ring opening in DMSO at rt to allow equilibrium with the corresponding dihydrofurans, **73a-73c** (Scheme 14 and Table 1).[16] A push-pull mechanism is the driving force that is responsible for the ring cleavage.

Although this equilibrium reaction is not much useful synthetically as revealed from the percentage of conversion, it is important to note that the relative stereochemistry of the substituents in the starting cyclopropane is conserved in the product.



72a-72c 73a-73c

72a: R = $CH(OCH_3)_2$, X = E = CO_2Me
72b: R = H, X = E = CO_2Me
72c: R = X = E = CO_2Me

Scheme 14

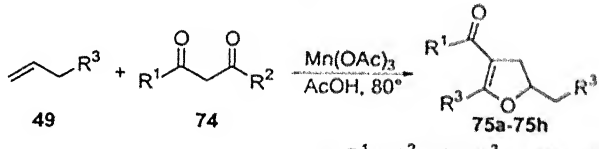
Table 1

Equilibrium	DMSO, 25 °C	C_6D_6
72a ⇌ **73a**	48 h (50/50)	48 h at 60 °C (15/85)
72b ⇌ **73b**	1 h (20/80)	48 h at 20 °C (50/50)
72c ⇌ **73c**	53 h (20/80)	28 h at 80 °C (45/55)

In a modification of the method of Scott and Cotton, Fukuzawa *et al.* used SmI_2 in place of Zn for the generation of the ketocarbenoid from α,α-dibromodeoxybenzoin and improved upon the yields of the products.[17] A variety of olefins underwent 1,3-dipolar addition regio- and stereo-selectively with the ketocarbenoid to give substituted dihydrofurans in moderate to good yields. The major disadvantage of this method was that it was not inapplicable to alkyl-substituted alkenes, as the reaction always required a phenyl or a double bond in conjugation with the reacting double bond.

Hwu and co-workers have exploited the oxidizing ability of $Mn(OAc)_3$ in the synthesis of dihydrofurans from allylsilanes and β-

dicarbonyls (Scheme 15).[18] The reaction involves the addition of α-carboradical, generated from the reaction of a β-dicarbonyl compound, **74**, with $Mn(OAc)_3$, to allylsilanes to give silicon stabilized β-carboradical. It is followed by an intramolecular attack on the radical center by one of the carbonyl oxygen to generate another more stable carboradical. This undergoes subsequent oxidation by $Mn(OAc)_3$ and elimination of the α-hydrogen to give dihydrofuran **75**. When CAN was used in the place of $Mn(OAc)_3$ as an oxidant, dihydrofurans were obtained only with the bulky silyl substituted allylsilanes. With allylsilanes bearing sterically less bulky silyl substituents such as trimethylsilyl, simple allylated dicarbonyls were the sole products. This is because CAN is a more powerful oxidant than $Mn(OAc)_3$ and it oxidized the β-silyl carboradical into β-silyl carbocation which underwent facile elimination before the cyclization could take place when the silyl substituents were less bulky.



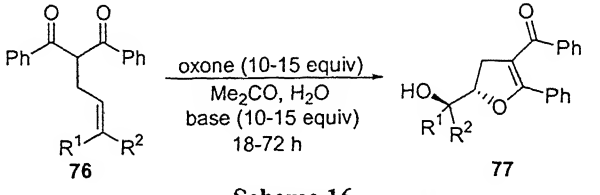
49 **74** **75a-75h**

a: $R^1 = R^2 = Ph$, $R^3 = SiMe_3$, 91%
b: R^1-$R^2 = (CH_2)_3$, $R^3 = SiMe_3$, 88%
c: $R^1 = OEt$, $R^2 = Me$, $R^3 = SiMe_3$, 85%
d: $R^1 = OEt$, $R^2 = n$-Pr, $R^3 = SiMe_3$, 73%
e: $R^1 = OEt$, $R^2 = Me$, $R^3 = SiMe_2Ph$, 82%
f: $R^1 = R^2 = Ph$, $R^3 = Si(i\text{-}Pr)_3$, 67%
g: $R^1 = OEt$, $R^2 = Me$, $R^3 = Si(i\text{-}Pr)_3$, 76%

Scheme 15

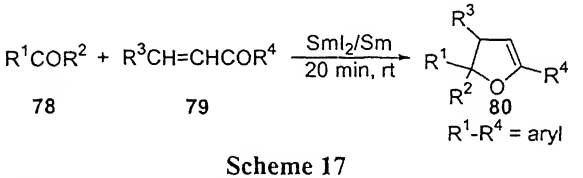
Antonioletti *et al.* have developed a simple one step protocol for making dihydrofurans.[19] It involves one pot epoxidation of 2-allyl-1,3-dicarbonyl compounds, **76**, by *in situ* generated DMD

(oxone/acetone/water) followed by base ($NaHCO_3$ or Na_2CO_3) promoted intramolecular ring opening of the epoxide by the oxyanion of the enolate (Scheme 16). The intramolecular attack is highly regioselective in following a 5-*exo*-tet process. This protocol, however, suffers from the often long times required.



Scheme 16

Diaryl ketones and chalcones undergo reductive cyclization on treatment with SmI_2/Sm in anhydrous THF at rt (Scheme 17).[20] The scope of this method is limited as it is specific and applicable to the reactions involving only chalcones and diaryl ketones in combination. Even if one of the reactants had alkyl groups instead of the aryl groups, dihydrofuran formation was not observed. Also, the reaction required a combination of SmI_2 and Sm for good yields. The yields were generally poor when SmI_2 was used alone.

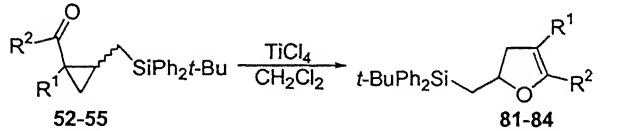


Scheme 17

1.2.3.1 Results and Discussion

In our preliminary experiments, we reacted the cyclopropane derivative **52** bearing two methyl ester functions with 2-phenylpropanal in the presence of $TiCl_4$ at 0 °C to rt. Interestingly, we obtained only the

dihydrofuran **81** (89% yield); products like **44** and **45** (Scheme 9) were not formed. Our all attempts at changing the reaction temperature and the order of addition to obtain **44/45**-like products resulted in the formation of only the dihydrofuran **81**, always in excellent yields. When **52** was treated with $TiCl_4$ alone at –30 °C, the yield of **81** was as high as 96% (Table 2, entry 1). Since dihydrofurans are synthetically important materials and the known protocols to prepare them often suffered from undesirable reaction conditions and the lack of applicability to diverse substituent types, we decided to pursue the dihydrofuran formation with other cyclopropane derivatives as well.[21] We treated **53-57** carrying different electron-withdrawing groups with $TiCl_4$ (Scheme 18). Cyclopropanes bearing two electron-attracting groups, **53-55**, underwent facile regioselective ring opening to furnish substituted dihydrofurans in good to excellent yields (entries 2-4). A ketone enolate cyclized in preference to an ester enolate (entry 3). This is in accordance with the results observed in the copper-catalyzed 1,3-dipolar addition of diazomethylacetoacetate to electron-rich olefins such as vinyl ethers.[15]



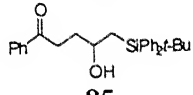
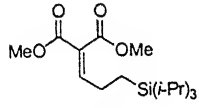
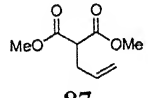
52-55 **81-84**

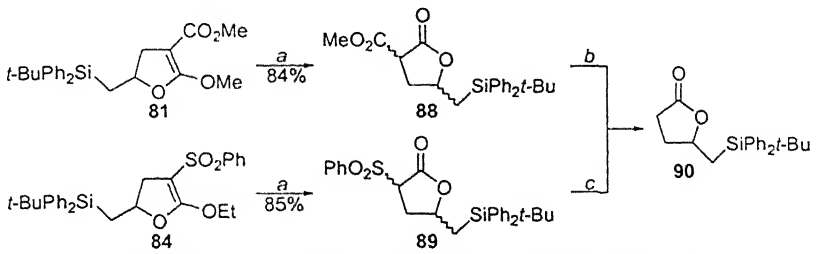
81: $R^1 = CO_2Me$, $R^2 = OMe$
82: $R^1 = COMe$, $R^2 = Me$
83: $R^1 = CO_2Et$, $R^2 = Me$
84: $R^1 = SO_2Ph$, $R^2 = OEt$

Scheme 18. $TiCl_4$-promoted formation of dihydrofurans

The structures of the compounds **82** and **83** were confirmed by comparison of the spectral data available for compounds that differed only in the silyl substituents.[18] The structures of **81** and **84** were confirmed by transforming them into 5-(*tert*-butyldiphenylsilyl)methyl-γ-lactone **90** (Scheme 19) by acid hydrolysis followed by dealkyldecarboxylation using NaCl/DMSO/H_2O[22] and desulfonation using 5% Na(Hg)/MeOH[23], respectively.

Table 2. Results of $TiCl_4$-promoted ring opening of **52-59**

Entry	Silane	Temp °C	Time (h)	Product(s)	Yield(%)
1	**52**	-30	3	**81**	96
2	**53**	0 to rt	3	**82**	81
3	**54**	-30	1/6	**83**	70
4	**55**	-30 to rt	8	**84**	75
5	**56**	-30	1	 **85**	45
6	**57**	0 to rt	21	no reaction	
7	**58**	0 to rt	6	 **86**	54
				 **87**	26
8	**59**	0 to rt	6	**87**	97

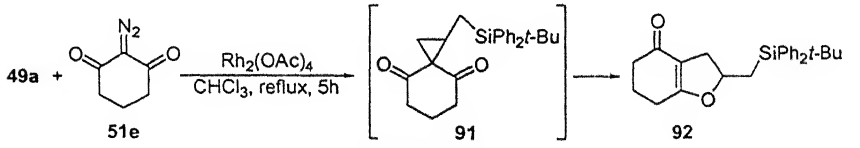


Reagents and conditions: *a*, 10% $HClO_4$/THF,reflux, 5 h; *b*, NaCl/H_2O, DMSO, reflux, 4 h, 85%; *c*, 5% Na(Hg), MeOH, rt, 4 h, 74%.

Scheme 19. Conversion of **81** and **82** into γ-lactone **90**

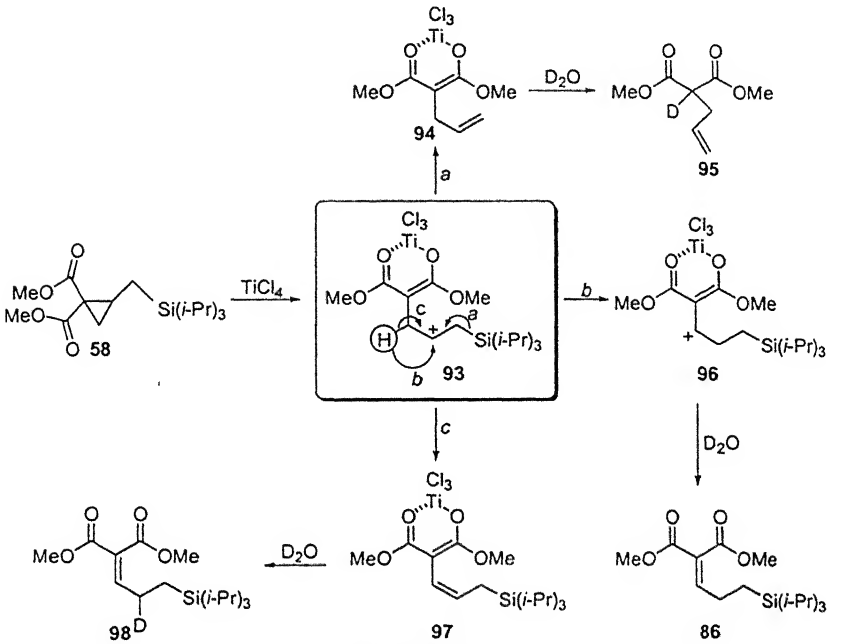
No ring cleavage was observed even after stirring for prolonged time at rt when the cycopropane ring had a single ester function (entry 6). The starting ester was recovered quantitatively. This may be due to the insufficient activation of the ring with a single ester function. Contrary to this, a single phenyl ketone in **56** brought about the ring cleavage smoothly to furnish (3-hydroxy-4-*tert*-butyldiphenylsilyl)butyl phenyl ketone, **85**, in 45% yield. It is significant to note that the enolate did not cyclize on the incipient carbocation to give the desired dihydrofuran.

The above methodology was extended to prepare bicyclic ether as well. The cyclopropane **91** was so reactive that it furnished the desired product under the conditions of its formation itself (Scheme 20). The use of Lewis acid was not necessary. This high reactivity may be attributed to the ring strain present in **91**.



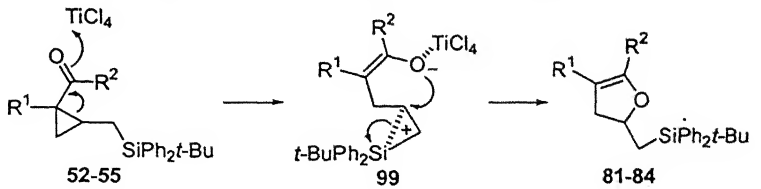
Scheme 20

To examine the role of bulky silyl substituents, we treated cyclopropane derivative **58** bearing comparatively less bulky triisopropylsilyl function. It did not give the expected dihydrofuran, instead, to our surprise, it gave a mixture of the α,β-unsaturated diester **86** and the α-allylated dimethylmalonate **87** in 54% and 26% yields, respectively. The formation of the allylated product **87** is easily explained by the elimination of the silicon function on attack by chloride ion. The formation of **86** requires either migration of a hydrogen from the carbon γ to the silicon to the β-carbocation (Scheme 21, **93**, pathway *b*) to generate **96** or elimination of a γ-hydrogen as H^+ to result in the dienolate **97** (**93**, pathway *c*) which subsequently gave **86** upon aq workup. To determine the actual pathway involved, we quenched the reaction with D_2O as only the species **94** and **97** are expected to be quenched by deuterium to give the deuterated compounds **95** and **98**, respectively. We observed deuteration only in the allylated product **87** at the α carbon. This experiment gives enough evidence for the pathway *b* that is responsible for the formation of **86** *via* **96**. As the triisopropylsilyl function favored considerably its elimination, we prepared the cyclopropane derivative **59** bearing still less bulky phenyldimethylsilyl function and subjected it to $TiCl_4$-promoted ring opening. It furnished the allylated dimethyl malonate **87** in nearly quantitative yield by the extrusion of the phenyldimethylsilyl function. These experiments strongly indicate the importance of bulky *tert*-butyldiphenylsilyl substituent in the formation of dihydrofurans.



Scheme 21

The formation of dihydrofurans proceeds presumably through a 5-*exo*-trig cyclization of the titanium enolate on the silicon-stabilized carbocation **99** that is formed from ring opening (Scheme 22).



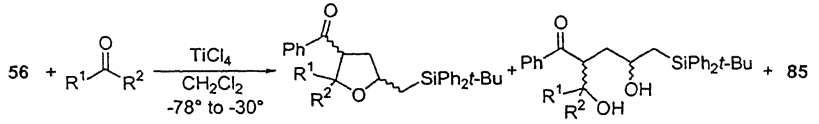
Scheme 22. Mechanism of dihydrofuran formation

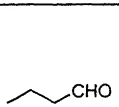
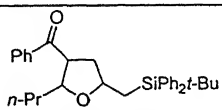
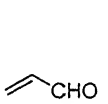
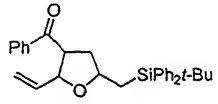
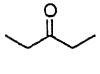
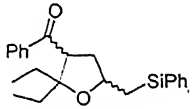
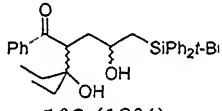
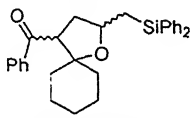
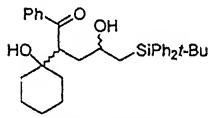
In the above reactions, formation of other possible products such as cyclobutane derivatives by ring expansion, intermolecular addition products and dihydropyrans were not observed.

1.2.4 Application of phenyl ketone substituted cyclopropane 56 in the synthesis of substituted tetrahydrofurans

Since the enolate generated from the phenyl ketone substituted cyclopropane **56** upon treatment with $TiCl_4$ did not cyclize intramolecularly to give the corresponding dihydrofuran derivative, it offered an opportunity to explore its reactions with other electrophiles such as carbonyls since an intermolecular reaction is expected to result in either tetrahydrofuran or tetrahydropyran as in Scheme 9 (*vide infra*). We treated **56** with butyraldehyde in the presence of $TiCl_4$. Indeed, the expected tetrahydrofuran derivative **100** was obtained as a mixture of two diastereomers with a ratio of 4.3:1 in 36% yield. The formation of tetrahydropyran derivative was not observed. The silicon function in the diastereomeric mixture was converted into a hydroxyl function by a two-step protocol[10] (Scheme 23) to obtain **106**. The major isomer **106a** was separated from the mixture and its stereochemistry was deduced from a series of 1D-nOe experiments and by comparison of the spectral data with those of similar known compounds.[24] The *trans* relationship of the phenyl ketone function with the propyl substituent was established from the nOe enhancement of H_a on irradiation of H_c. Likewise, the *cis* relationship of the phenyl ketone function with the hydroxymethyl group was derived from two separate nOe experiments. The signal for H_d enhanced when H_c and H_f were irradiated, individually. This indicates an all *cis* relationship of H_c, H_d, and H_f. This, in turn, proves the *cis* relationship between the phenyl ketone and the hydroxymethyl substituents (Figure 5).

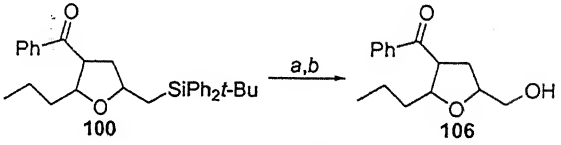
Table 2. Results of the reactions of cyclopropane derivative **56** with aldehydes and ketones



Entry	R^1 R^2	Product(s) and yields	
1		 **100** (36%) 4.3:1	**85** (21%)
2		 **101** (24%) 4.5:1	**85** (18%)
3		 **102** (20%) 2.4:1  **103** (18%) 1:1.7 (lp:mp)	**85** (26%)
4		 **104** (23%) 1.9:1  **105** (27%) 3.2:1 (lp:mp)	**85** (13%)

The reaction of **56** with acrolein furnished a diastereomeric mixture of the corresponding tetrahydrofuran derivative **101**. The diastereomeric ratio was calculated as 4.5:1 from the ^{1}H integrals. The enolate generated from **56** reacted with ketones as well. Symmetrical diketones such as 3-pentanone and cyclohexanone gave diastereomeric

mixtures of **102** and **104**, respectively. In both the cases, the corresponding diastereomeric diols **103** and **105**, respectively, were also formed. These diastereomeric diols were separated from each other and characterized by spectral means. However, no attempt was made to establish the relationship of the stereogenic centers. It is significant to note that the similar diols that formed from the reactions with butyraldehyde and acrolein (entries 1 and 2) were highly unstable as their spectra were always complicated due to decomposition. In all the reactions, small amounts of 3-hydroxy-4-*tert*-butyldiphenylsilylbutyl phenyl ketone, **85**, were also formed.

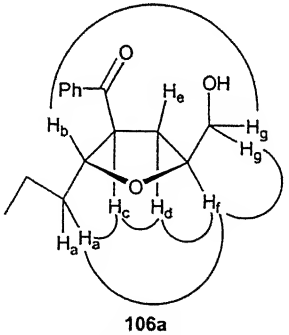


100 **106**

a. BF_3•2 AcOH, CH_2Cl_2, reflux, 7 h

b. H_2O_2, $NaHCO_3$, KH, THF/MeOH, reflux, 3 h

Scheme 23. Oxidative cleavage of silicon function in **98**



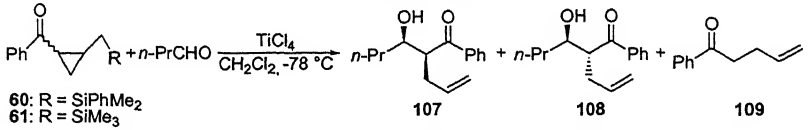
106a

Figure 5

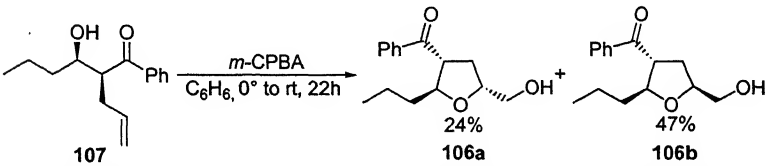
In order to study the importance of bulky silyl substituents in the present cyclization reactions, we reacted the cyclopropyl phenyl

ketones **60** and **61** bearing dimethylphenylsilyl and trimethylsilyl functions, respectively, as donor substituents with butyraldehyde. Interestingly, neither of these substrates gave the corresponding tetrahydrofuran material. However, β-hydroxy ketones **107** and **108** were obtained in good yields from both the reactions (Table 4). The ~ 4:1 ratio of the diastereomeric alcohols was obtained from ^{1}H NMR integrals and chromatographic separation. The hydroxyl and the allyl groups were *syn* to each other in the major diastereomer. This was confirmed by converting it into tetrahydrofuran derivative. The major diastereomer **107** gave, on treatment with *m*-CPBA[25] in benzene, a mixture of two separable tetrahydrofuran methanols in the ratio 1:2 (Scheme 24). The minor diastereomer had similar NMR pattern as that of the major isomer **106a** (Figure 5) obtained from **100** whose stereostructure was well established from nOe experiments (*vide infra*). Hence, the minor diastereomer was assigned the stereostructure **106a**. By default then, the major isomer was assigned the stereostructure **106b**. The *trans* relationship between the propyl and phenyl ketone functions in **106** was confirmed further from the fact that both the isomers, **106a** and **106b**, were stable to Et_3N-CH_2Cl_2; there was no epimerization.

Table 4. Results of the reactions of cyclopropane derivatives **60** and **61** with butyraldehyde



Silane	Products distribution (%)		
	107	**108**	**109**
60	59	14	15
61	56	14	13



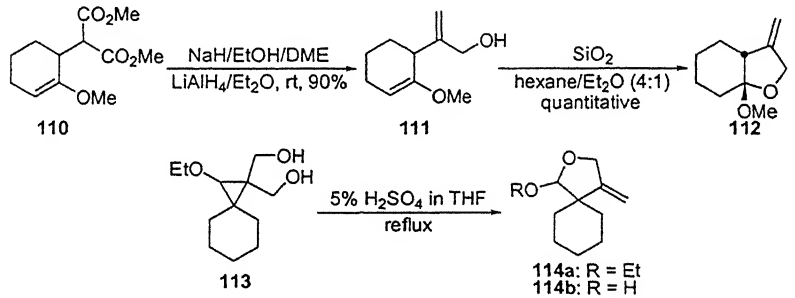
Scheme 24. Conversion of β-hydroxy ketone **107** into tetrahydrofuran derivatives

1.2.5 Synthesis of γ-methylene oxacycles and α– and β–ethylidene lactones *via* silicon-assisted ring opening of cyclopropyl carbinols

γ-Methylene oxacycles and α- and β-alkylidene lactones are widespread as subunits in a large number of biologically active natural products and therapeutic agents. The synthesis of these structural motifs in an efficient manner has received great interests. The α-methylene-γ-lactones are important. They have been synthesized in several ways and the reader is advised to consult reviews.[26] However, only a few methods are known for the syntheses of the other above-mentioned heterocycles.

Wenkert *et al.* synthesized the bicyclic and spirocyclic β-methylene oxacycles **112** and **114**, respectively, by making use of an

acid-promoted cyclization reaction as the key step.[27] Lithium aluminium hydride reduction of the sodio-enolate of the diester **110** led to the formation of the acid-labile allylic alcohol **111** which was converted into the bicyclic β-methylene tetrahydrofuran **112** over silica gel column. Acid-promoted ring opening and subsequent cyclization of the diol **113** resulted in the formation of the acetal **114a** and the hemiacetal **114b** in, respectively, 30 min and 24 h at reflux in 5% H_2SO_4 in THF (Scheme 25).



110 **111** **112**

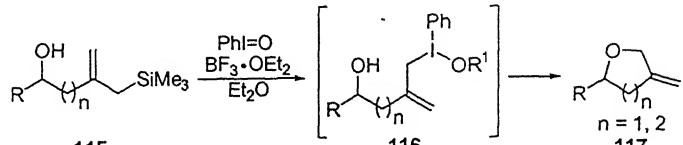
113

114a: R = Et
114b: R = H

Scheme 25

Hypervalent organoiodine compounds are useful mild oxidizing reagents. Ochiai *et al.* have exploited the high reactivity of alkylaryliodonium intermediate for the synthesis of β-methylene cyclic ethers. Easily obtainable allylsilanes **115** containing a suitably placed hydroxyl group gave, on treatment with iodosylbenzene in the presence of BF_3•OEt_2 in Et_2O, 5- and 6-membered β-methylene cyclic ethers in moderate yields. The reaction essentially involved the formation of highly reactive alkylaryliodonium intermediate **116** that underwent immediate intramolecular nucleophilic displacement of the

alkylaryliodonium group by the hydroxyl function to furnish the β-methylene cyclic ethers **117** (Scheme 26).

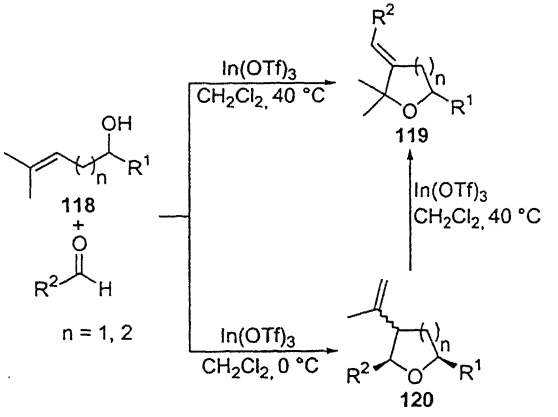


115 **116** **117**

R^1 = H·BF_3 or $SiMe_3$·BF_3

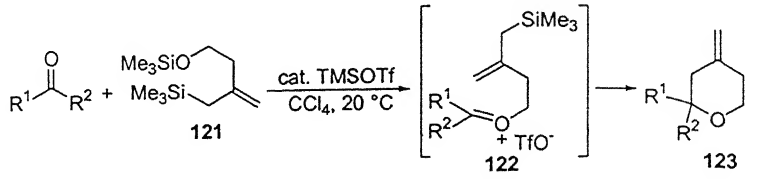
Scheme 26

Loh *et al.* have recently developed a $In(OTf)_3$-catalyzed (3,5) oxonium-ene cyclization for the construction of different multisubstituted oxacycles (Scheme 27) from the alkenol **118**.[29] The formation of tetrahydrofurans **120** was kinetically controlled and it took place at 0 °C. The thermodynamic β-methylene oxacycles **119** were formed at 40 °C only when n=1 (5 membered ring). The kinetic product **120** (n=1) underwent $In(OTf)_3$-catalyzed skeletal reorganization to give **119** (n=1) under thermal conditions. When n=2, only **120** was formed under both the conditions. The 2,3-*trans*-2,6-*cis* stereorelationship was maintained in tetrahydropyran products *via* a rigid six-membered chair like TS that had all the substituents in equatorial positions. A similar 2,3-*trans*-2,5-*cis* diastereoselectivity in tetrahydrofuran formation was poor due to the flexible five-membered TS.



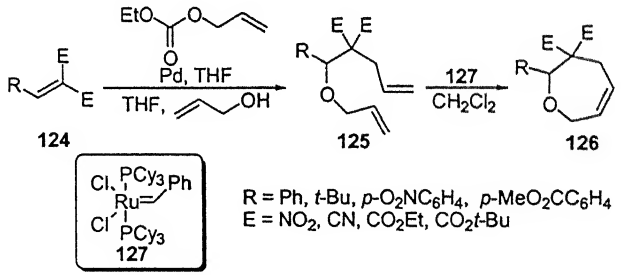
Scheme 27

Markó *et al.* have studied the Intramolecular Silyl Modified Sakurai (ISMS) reaction in the construction of tetrahydropyrans, spiroethers, and spiroketals (Scheme 28).[30] This reaction has found successful applications in the synthesis of a few natural products possessing these structural units. The ISMS reaction is catalyzed by TMSOTf and it probably involves the *in situ* generation of an oxonium ion intermediate **122**. At room temperature substrate **121** gave a mixture of exocyclic tetrahydropyran **123** and its corresponding internal olefin analog. The olefin migration in the product was found to be catalyzed by the TfOH generated during the progress of the reaction. The double bond migration was completely eliminated in the presence of another silyl ether such as $C_6H_{13}OTMS$ or C_2H_5OTMS in the reaction mixture. This method of constructing γ-methylene tetrahydropyran was used in the syntheses of a minor component of the rectal gland secretion of the female *Dacus oleae* fruit fly,[33a,b] eastern subunit of ambruticine,[30c] and a pseudomonic acid C analog.[30d]



Scheme 28

Ring-closing metathesis is one of the modern methodologies in constructing 5-, 6- and 7-membered rings with diverse functionalities from diolefins. Grubb's ruthenium-based organometallic alkylidene **127** finds enormous application in this reaction. Hauske *et al.* have recently utilized RCM in obtaining functionalized 7-membered ring allyl ethers.[33] Dienes **125**, which are easily accessible by the Pd-catalyzed alkoxyallylation of alkylidene active methylene compounds **124** by allyl alcohol were subjected to olefin metathesis in the presence of a catalytic amount of **127** to obtain **126** (Scheme 29).

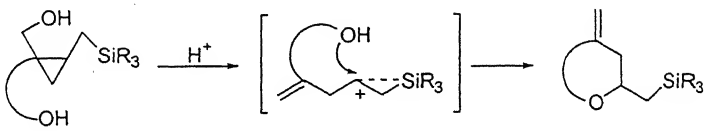


Scheme 29

1.2.5.1 Objectives

Encouraged from the successful and facile silicon-assisted ring opening of donor-acceptor substituted cyclopropanes in the syntheses of substituted dihydrofurans and tetrahydropyrans, we thought that the ring opening will also be facilitated by generating a carbocationic

center adjacent to the cyclopropane ring. A carbocationic center of this kind could be easily generated from the corresponding cyclopropylcarbinol by treating it with an acid. The intramolecular trapping of the ring-opened silicon-stabilized β-carbocation with a tethered hydroxyl function is expected to result γ-methylene oxacycles (Scheme 30).



Scheme 30

1.2.5.2 Background

Amongst the known cleavages of cyclopropane, acid-promoted cleavage of cyclopropylcarbinols has been extensively studied from both theoretical and synthetic viewpoints.[32] The initially formed cyclopropylcarbinyl cation can undergo either ring expansion to give cyclobutyl cation[33] or ring cleavage to result in a homo allyl cation[35] in order to relieve ring strain. Phenyl and alkoxy-containing cyclopropyl carbinols have been extensively studied as these groups facilitate the ring opening by stabilizing the resulting carbocation. The resulting carbocation could be trapped by nucleophiles for further synthetic manipulations.[34] Only the ring expansion reactions have been studied in great detail.

1.2.5.3 Starting Materials

To study the silicon-assisted ring opening and subsequent intramolecular trapping of the resultant ring-opened β-silyl carbocation

with a heteroatom, we prepared diols **128-130** and hydroxyesters **131** and **132** (Figure 6). The syntheses of the precursors, the diesters and the keto esters, are described in Section 1.2.2 of this chapter (*vide infra*). The diols **128**, **129a**, **130a**, **129b** and **130b** were obtained in excellent yields by $LiAlH_4$ reduction of the corresponding diesters **52**, **62**, and **63**, respectively. Selective reduction of the ketone function in the keto ester **54** was achieved with $NaBH_4$ in methanol to obtain **131a** and **131b**. $NaBH_4$ was found to be less successful in the reductions of both the isomers of **64** into **132a** and **132b**; only the spirocyclic-γ-lactones **139a** and **139b** were formed. The formation of the γ-lactones is not surprising as the initially formed γ-hydroxy ester is highly prone to lactonization under the reaction conditions. The required γ-hydroxy esters **132a** and **132b** were then obtained by reducing the corresponding isomers of **64** with $NaCNBH_3$ at pH 3-4. We focused our studies with the substrates possessing *tert*-butyldiphenylsilyl substituent as it worked well in the formation of dihydrofurans and tetrahydrofurans. The stereochemistries of the cyclopropane derivatives were discerned from 1D-nOe experiments on **129a**, **129b**, and **64b**.

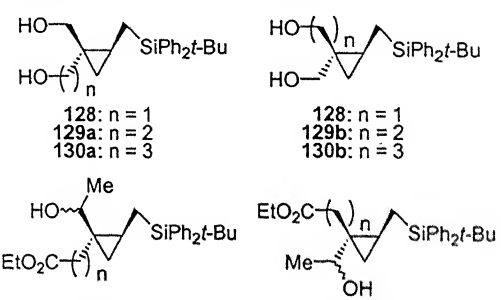


Figure 6. Structures of different cyclopropyl carbinols studied

The *syn* relationship of the *tert*-butyldiphenylsilylmethyl group with the hydroxymethyl group in **129a** (less polar) was established from the nOe enhancements of their methylene hydrogens, H_a and H_b. This was supported by the nOe enhancements of the cyclopropane methine hydrogen H_d and the methylene hydrogens H_c. On the other hand, in the more polar isomer **129b**, the same methine hydrogen H_d showed nOe enhancement of the methylene hydrogens H_a, indicating a *trans* relationship between the hydroxymethyl and the *tert*-butyldiphenylsilylmethyl substituents. The stereochemistryies of **130a**, and **130b** were derived from comparisons of ^1H signals and the polarity features (TLC) with those of **129a** and **129b**.

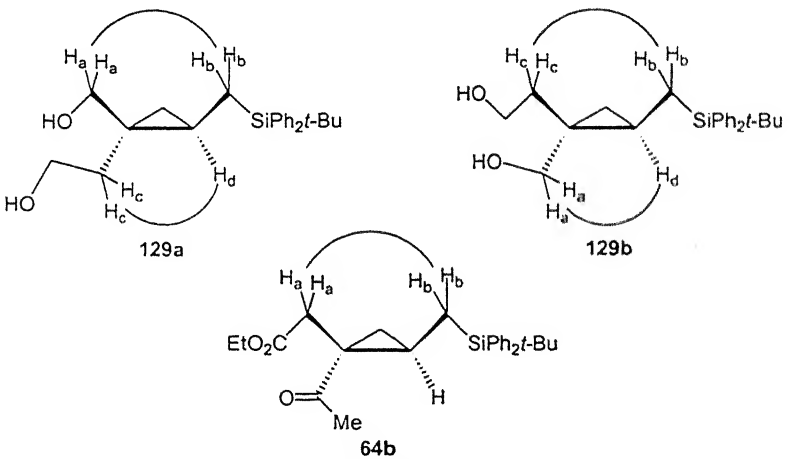


Figure 7

The stereo-relationship of the carboethoxymethyl function with the *tert*-butyldiphenylsilylmethyl group in the hydroxyester **132b** (more polar) was ascertained to be *syn* from nOe experiments carried out on its corresponding ketoester **64b**. The less polar isomer was assigned, by

default, the stereostructure shown in **132a**. The stereostructures of the hydroxyesters **131a** and **131b** were ascertained by comparison of their ^1H signals and the polarity features (TLC) with those of **132a** and **132b**.

The above stereochemical assignments of the compounds **131a**, **132a**, **131b**, and **132b** are further supported by the results obtained from the selective reduction of methyl ketone function in **54** and **64**. The less polar isomers of both **54** and **64** gave predominantly one diastereomeric alcohol while the corresponding more polar isomers gave a 1:1.6 and 1:1 mixtures of diastereomeric alcohols respectively. Effective blocking of one of the faces of prochiral methyl ketone by the bulky silyl substituent when these substituents are *syn* could be the reason for the very high selectivities in the reductions of the less polar isomers of **54** and **64**.

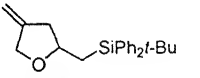
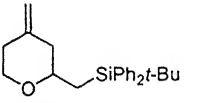
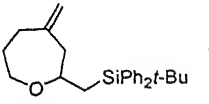
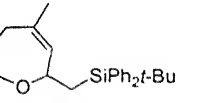
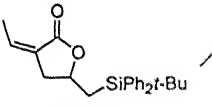
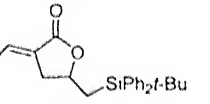
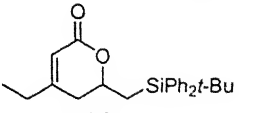
1.2.5.4 Results and Discussion

In exploratory experiments, we tried the ring cleavage of the diol **128** with selected protic and Lewis acids. The reaction with $SnCl_4$ in CH_3NO_2 and TFA in CH_2Cl_2 were unsuccessful as several products were formed with $SnCl_4$ and there was no reaction in the presence of TFA. Reactions with 5% H_2SO_4 in THF and *p*-TSA in benzene under reflux were only partially successful. The yield of the tetrahydrofuran derivative **133** was poor (~50%) with both the proton sources. We then studied the reaction of the diol **128** with *p*-TSA in THF. Smooth and regioselective ring opening took place at reflux to furnish **133** in 86% yield. Encouraged from this result, we set out to study the scope of the reaction and prepared the other diols **129** and **130** (both isomers) by

increasing the length of one of the two hydroxy methyl side chains. We aimed to synthesize γ-methylenetetrahydropyran and γ-methyleneoxepan as these skeletons are found in many useful natural products. When n=2 (**129a** and **129b**), γ-methylene tetrahydropyran **134** was obtained in good yield (Table 5, entries 2 and 3). Both the isomers **130a** and **130b** (n=3) gave a mixture of **135** and **136**. The latter is formed by isomerization of the former under the acidic reaction conditions.

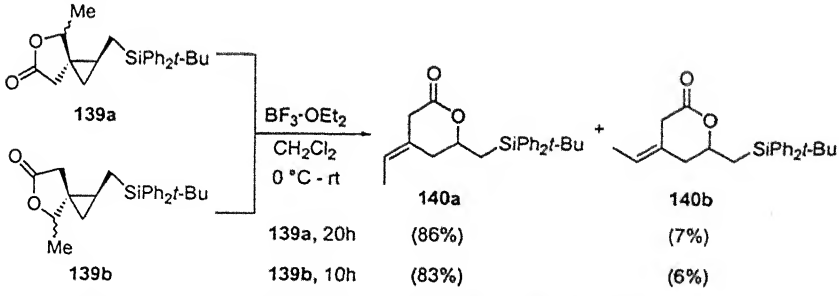
To exploit the present methodology further, we reacted the substrates **131a**, **132a**, **131b**, and **132b** that bear one hydroxyl and one-ester functions. Lactones were expected to form by the attack of the ester function on the β-silyl cation in the ring-opened species. The substrates **131a** and **131b** gave, on treatment with *p*-TSA in THF at reflux, a mixture of α-ethylidene-γ-lactones **137a** and **137b** (entries 6 and 7). The isomers were separated and the olefin geometries were discerned from the relative ^{1}H signal positions of the vinylic methyl and the vinylic hydrogen. The vinylic methyl in **137a** appeared much downfield (δ 2.07, d, J = 7.3 Hz) compared to that in **137b** (δ 1.57-1.54, td, J = 7.1, 1.7 Hz). On the other hand, the vinylic hydrogen in **137a** appeared upfield (δ 6.01-5.95, m) compared to that in **137b** (δ 6.64-6.58, m). The downfield appearance of signals for the vinylic methyl in **137a** and the vinylic hydrogen in **137b** compared to those in the other isomers is due to the anisotropic effect of the carbonyl function.

Table 5. Conversion of cyclopropyl carbinols **128-132** into different γ-methylene oxacycles and lactones

Entry	Silane	Time (h)	Product(s) and yields
			 **133**
1	**128**	3	86%
			 **134**
2	**129a**	7	72%
3	**129b**	6	74%
			 **135**  **136**
4	**130a**	3	31% 58%
5	**130b**	8	16% 64%
			 **137a**  **137b**
6	**131a**	33	33% 46%
7	**131b**	18	18% 69%
			 **138**
8	**132a**	26	81%
9	**132b**	13	92%

The isomers **132a** and **132b** furnished their corresponding spirocyclic γ-lactones **139a** and **139b** on reflux with *p*-TSA in THF for

2 and 1 h respectively, in >95% yield. It is important to note that the diastereomeric ratio of the starting hydroxy esters **132a** and **132b** is maintained in their respective products **139a** and **139b** also. On further reflux with *p*-TSA in THF, these spirocyclic γ-lactones **139a** and **139b** were transformed into the α,β-unsaturated δ-lactone **138** *via* isomerization of the primary products β-ethylidene-δ-lactones **140a** and **140b**. In order to obtain the desired β-ethylidene-δ-lactones **140a** and **140b**, we treated separately the spirocyclic γ-lactones **139a** and **139b** with $BF_3{\cdot}OEt_2$ in anhydrous CH_2Cl_2 to effect the cyclopropane ring opening. Indeed, the expected products **140a** and **140b** were obtained in excellent yields (Scheme 31). It is noteworthy that this reaction is highly stereoselective; **140a** was formed 12 times more than **140b**. The geometry of the olefin in **140a** was discerned from nOe experiments; the olefinic hydrogen showed nOe enhancement of the α-methylene hydrogens.



Scheme 31. Conversion of spirocyclic lactones **139a** and **139b** into β-ethylidene-δ-lactone **140a** and **140b**.

1.3 Conclusions

The donor-acceptor substituted cyclopropanes bearing trialkylsilylmethyl function as the donor function undergo facile and regioselective silicon-assisted ring opening on treatment with $TiCl_4$ under mild conditions. Cyclopropanes bearing two electron-attracting groups with vicinally substituted *tert*-butyldiphenylsilylmethyl group are easily transformed into substituted dihydrofurans. The enolate generated from the cyclopropane derivative **56** containing a single phenyl ketone moiety prefers to undergo an intermolecular [3+2] cyclization with aldehydes and ketones. The results of this intermolecular cyclization are promising even though the yields of the tetrahydrofuran derivatives are low. The steric bulk of the silyl substituents plays a crucial role in both the dihydrofuran and tetrahydrofuran formations. Cyclopropyl carbinols bearing *tert*-butyldiphenylsilylmethyl group undergo similar silicon-assisted ring opening with *p*-TSA. Intramolecular trapping of the resulting β-silyl carbocations with heteroatoms could be effectively used to generate a wide range of synthetically important molecular skeletons such as 5-, 6-, and 7-membered γ-methylene cyclic ethers, α-ethylidene-γ-lactones, and β-ethylidene-δ-lactones.

1.4 Experimental

General

^1H and ^{13}C spectra were recorded on JEOL JNM-LA400 and JEOL-60 series of instruments using solutions in $CDCl_3$ and CCl_4. The ^1H and ^{13}C spectra were referred, respectively, to TMS used as an

internal standard and the central line for $CDCl_3$. Chemical shifts are reported in δ, and coupling constants in Hz. IR spectra were recorded on Bruker Vector 22 FT-IR spectrometer. Elemental (C, H, N) analyses were done on Perkin-Elmer 240-C automatic elemental analyzer. Allyltrimethylsilane and chlorodimethylphenylsilane were purchased from Aldrich and used as such. Chlorotriisopropylsilane, *tert*-butylchlorodiphenylsilane and $Rh_2(OAc)_4$ were purchased from Lancaster and used as received. All the reactions were carried out using freshly distilled and dry solvents from solvent stills. Reagent grade solvents were procured from S. D. Fine Chem. Ltd. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen atmosphere. Dichloromethane and chloroform were distilled from CaH_2. Column chromatography was performed over silica gel (100-200 mesh) from Acme Chemicals using hexanes and ethyl acetate mixtures as eluent. The separation of isomers and their rigorous purification were achieved by radial chromatography using plates coated with silica gel PF_{254} (E-Merck). Solvents were removed under reduced pressure on a rotovap. Organic extracts were dried with anhydrous Na_2SO_4. The visualization of spots on TLC plates was effected by uv illumination, exposure to iodine vapor, DNP in 10% H_2SO_4 in ethanol, and heating the plates sprayed with 10% H_2SO_4 in ethanol.

***p*-Tolunesulfonyl azide.** To a solution of *p*-TSA (9.5 g, 50 mmol) in ethanol (65 mL) and water (7.5 mL), NaN_3 (3.6 g, 55 mmol) was added in portions. The reaction mixture was stirred at rt for 3 h. Most of the solvent was removed. The residue was mixed with water (70 mL) in a

separatory funnel and the oil was separated. The aq layer was extracted with CH_2Cl_2 (3 x 15 mL) and the extracts were mixed with the oil. The combined organic extracts were dried and concentrated to obtain *p*-toluenesulfonyl azide (9.2 g, 94%) as a colorless oil. ^{1}H NMR (60 MHz, CCl_4): δ 7.8 (2H, d, J = 8.0 Hz), 7.4 (2H, d, J = 9.0 Hz), 2.5 (3H, s).

Methanesulfonyl azide.[12a] To a stirred solution of methanesulfonyl chloride (11.5 g, 100 mmol) in methanol (40 mL), NaN_3 (8.5 g, 130 mmol) was added in portions. After stirring at rt for 3 h, most of the solvent was removed. The residue was mixed with water (100 mL) and the oily layer was separated using a separatory funnel. The aq layer was extracted with CH_2Cl_2 (3 x 20 mL) and the extracts were mixed with the oil. The combined organic extracts were dried and concentrated to get methanesulfonyl azide (11 g, 90.5%) as a colorless oil. ^{1}H NMR (60 MHz, $CHCl_3$): δ 3.5 (s)

Preparation of allylsilanes (49a-49c)

Allyl-*tert*-butyldiphenylsilane 49a.[11] To a stirred suspension of activated Mg turnings (0.912 g, 37.5 mmol) in anhydrous THF (10 mL) containing a crystal of iodine, allyl chloride (2.45 mL, 30 mmol) in anhydrous THF (30 mL) was added slowly over a period of 2 h at 0 °C. The reaction mixture was stirred further until most of the magnesium had reacted. Now, *tert*-butylchlorodiphenylsilane (3.9 mL, 15 mmol) in anhydrous THF (20 mL) was added slowly. The reaction mixture was stirred vigorously at rt for 2 h and then refluxed for 3 h. The reaction mixture was poured into aq NH_4Cl and it was extracted with hexanes (4

x 30 mL). The combined organic extracts were washed with brine, dried and the solvents were removed to obtain the crude product. It was purified by silica gel column chromatography (hexanes) to obtain pure allyl-*tert*-butyldiphenylsilane (4.2 g, quantitative). ^{1}H NMR (60 MHz, CCl_4): δ 7.7-7.0 (10H, m), 5.9-5.3 (1H, m), 5.0-4.6 (2H, m), 2.1 (2H, d, J = 8.0 Hz), 1.05 (9H, s).

The above procedure was followed for the preparation of **49b** and **49c**.

49b.[11] 96%, colorless liquid. ^{1}H NMR (60 MHz, CCl_4): δ 6.0-5.4 (1H, m), 5.0-4.6 (2H, m), 1.6 (2H, d, J = 8.0 Hz), 1.0 (21H, s).

49c.[11] 94%, colorless liquid: ^{1}H NMR (60 MHz, CCl_4): δ 7.4-6.9 (5H, m), 5.9-5.1 (1H, m), 4.8-4.4 (2H, m), 1.5 (2H, d, J = 8.0 Hz), 0.0 (6H, s).

Preparation of α-diazocompounds 51a-51e[12]

51a. To a mixture of dimethyl malonate (2.64 g, 20 mmol) and *p*-toluenesulfonyl azide (3.94 g, 20 mmol) in anhydrous CH_3CN (20 mL), a solution of Et_3N (2.8 mL, 20 mmol) in anhydrous CH_3CN (10 mL) was added slowly at rt. The addition caused a little warming of the reaction mixture and it turned yellow. After stirring for 3 h, the solvent was removed. The residue was mixed with Et_2O (40 mL) and washed with solutions of KOH in water (1.2 g in 15 mL and 0.2 g in 10 mL) and water (10 mL), successively. The Et_2O solution was dried and the solvents were removed to obtain the crude product. A quick filtration through a silica gel column furnished pure dimethyl α-diazomalonate, 2.6 g, 82%, thick pale yellow oil. ^{1}H NMR (60 MHz, CCl_4): δ 3.9 (s).

The above procedure was followed to obtain **51b-51e**.

51b. 68%, yellow oil. ^{1}H NMR (60 MHz, CCl_4): δ 2.3 (s).

51c. 74%, yellow oil. ^{1}H NMR (60 MHz, CCl_4): δ 4.1 (2H, q, J = 7.0 Hz), 2.3 (3H, s), 1.3 (3H, t, J = 7.0 Hz).

51d. 83%, yellow oil. ^{1}H NMR (60 MHz, CCl_4): δ 8.3-8.0 (2H, m), 7.8-7.5 (3H, m), 4.2 (2H, q, J = 8.0 Hz), 1.2 (3H, t, J = 8.0 Hz).

51e. 63%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (2H, t, J = 6.5 Hz), 2.06 (1H, quintet, J = 6.5 Hz).

51f.[12d] To a moisture free solution of diazomethane (2.8 g, 60 mmol) in Et_2O (100 mL), a solution of benzoyl chloride (2.1 mL, 18 mmol) in Et_2O (20 mL) was added slowly at 0 °C. The reaction mixture was allowed to warm up to rt and stirred overnight. Solvent removal and purification by silica gel column chromatography furnished pure **51f**, 2.41 g, 95%, low melting yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.76 (2H, m), 7.53-7.47 (1H, m), 7.43-7.37 (2H, m), 6.01 (1H, s).

51g.[12c] To a solution of ethyl α-diazoacetoacetate (2.4 g, 15.3 mmol) in ethanol (5 mL) stirred in an ice bath, a solution of NaOEt (prepared from 0.352 g of Na metal and 5 mL of EtOH) was added over a period of 30 min. After the addition was complete, the reaction mixture was stirred at the same temperature for an additional 30 min. The red colored reaction mixture was taken in ice-cold water (30 mL) and was extracted with Et_2O (20 mL). The aq phase was saturated with NaCl and extracted with Et_2O (3 x 15 mL). The combined etheral extracts were washed with water (20 mL) and dried. Solvent removal and rapid purification through a silica gel column (EtOAc/hexanes) furnished

pure ethyl α-diazoacetate, 1.17 g, 73%, yellow oil. ^{1}H NMR (60 MHz, CCl_4): δ 4.8 (1H, s), 4.6 (2H, q, J = 7.0 Hz), 1.3 (3H, t, J = 7.0 Hz).

51h.[12e] To a suspension of NaH (50%, 0.29 g, 6 mmol) in anhydrous THF (7 mL), a solution of ethyl acetoacetate (0.64 mL, 5 mmol) in anhydrous THF (8 mL) was added slowly at 0 °C. After stirring for an additional 30 min at rt, a solution of ethyl bromoacetate (0.61 mL, 5.5 mmol) in anhydrous THF (5 mL) was added and stirred for 8 h. The reaction mixture was then cooled in an ice bath and NaH (50%, 0.384 g, 8 mmol) was added to it in portions. After the effervescence had ceased, a solution of methanesulfonyl azide (0.605 g, 5.5 mmol) in anhydrous THF (5 mL) was added to it when the reaction mixture turned yellow. Et_2O (50 mL) was added to the reaction mixture and the etheral layer was washed with aq 5% KOH (2 x 10 mL) and water (10 mL), successively. The combined organic extracts were washed with brine, dried, and concentrated to give a residue which, on quick purification by silica gel column, furnished **51h**, 0.598 g, 60%, viscous yellow oil. ^{1}H NMR (60 MHz, CCl_4): δ 4.3 (2H, q, J = 7.0 Hz), 4.2 (2H, q, J = 7.0 Hz), 3.3 (2H, s), 1.3 (6H, t, J = 7.0 Hz).

51i.[12e] The procedure used for the preparation of **51h** above was followed with ethyl 3-bromopropionate in the place of ethyl bromoacetate, 56%, viscous yellow liquid. ^{1}H NMR (400 MHz, $CHCl_3$): δ 4.22 (2H, q, J = 7.1 Hz), 4.16 (2H, q, J = 7.1 Hz), 2.63-2.55 (4H, m), 1.28 (3H, t, J = 7.1 Hz), 1.27 (3H, t, J = 7.1 Hz).

51j.[12e] The Procedure used for the preparation of **51h** was followed with acetylacetone in the place of ethyl acetoacetate, 84%, viscous

yellow liquid. ^{1}H NMR (400 MHz, $CHCl_3$): δ 4.19 (2H, q, J = 7.1 Hz), 3.36 (2H, s), 2.28 (3H, s), 1.28 (3H, t, J = 7.1 Hz).

General procedure for cyclopropanation of allylsilanes (49a-49d) with diazo compounds (51a-51j)

Method A: To a stirred solution of the allylsilane (4 mmol) and $Rh_2(OAc)_4$ (0.0086 g, 0.02 mmol) in anhydrous $CHCl_3$ (0.5 mL), a solution of the diazo compound (2 mmol) in $CHCl_3$ (2 mL) was added over a period of 10 h using a syringe pump under nitrogen atmosphere at rt. The reaction mixture was stirred further for 5 h and the solvent was removed. The residue was chromatographed to obtain the pure product and also the unreacted allylsilane.[36]

Method b: To a refluxing solution of allylsilane (4 mmol) and $Rh_2(OAc)_4$ (0.0086 g, 0.02 mmol) in anhydrous $CHCl_3$ (0.5 mL), a solution of the diazo compound (2 mmol) in $CHCl_3$ (2 mL) was added over a period of 6 h using a syringe pump under nitrogen atmosphere. After the addition was over, reflux was continued for another 5 h and the solvent was removed. The residue was chromatographed to obtain the pure product and also the unreacted allylsilane.[36]

52. Method *b* was followed. 87%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.59 (4H, m), 7.40-7.33 (6H, m), 3.78 (3H, s), 3.63 (3H, s), 1.96-1.88 (1H, m), 1.65-1.61 (1H, dd, J = 14.6, 2.7 Hz), 1.20-1.13 (2H, m), 1.05 (9H, s), 0.80-0.73 (1H, dd, J = 14.6, 11.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 168.6, 136.0, 135.9, 133.9, 133.7, 129.2, 127.7, 127.6, 52.43, 52.36, 35.2, 27.7, 25.8, 23.5, 18.0, 10.0.

53. Method *a* was followed. 33%, viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.59 (4H, m), 7.44-7.34 (6H, m), 2.30 (3H, s), 1.95-1.86 (1H, m), 1.92 (3H, s), 1.43-1.39 (1H, dd, J = 14.7, 3.2 Hz), 1.36-1.33 (1H, dd, J = 7.7, 5.0 Hz), 1.09-1.06 (1H, dd, J = 9.0, 4.9 Hz), 1.04 (9H, s), 0.84-0.78 (1H, dd, J = 14.7, 11.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 203.6, 136.0, 135.9, 133.7, 129.39, 129.37, 127.8, 127.7, 50.8, 31.2, 27.8, 27.7, 26.6, 22.8, 18.1, 9.3.

54. Method *a* was followed. 38%, viscous liquid (1.3:1 mixture of more polar and less polar isomers).

54 (less polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.59 (4H, m), 7.41-7.33 (6H, m), 4.17-4.04 (2H, m), 2.33 (3H, s), 2.07-1.98 (1H, m), 1.37-1.32 (2H, m), 1.19 (3H, t, J = 7.2 Hz), 1.14-1.10 (1H, dd, J = 9.2, 4.4 Hz), 1.04 (9H, s), 0.92-0.86 (1H, dd, J = 14.8, 11.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 171.1, 136.1, 136.0, 134.0, 133.9, 129.3, 127.7, 127.6, 61.0, 41.9, 31.0, 29.1, 27.7, 23.1, 18.1, 14.0, 8.5.

54 (more polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.57 (4H, m), 7.40-7.33 (6H, m), 4.35-4.20 (2H, qq, J = 10.8, 7.1 Hz), 2.28 (3H, s), 1.99-1.91 (1H, m), 1.59-1.55 (1H, dd, J = 14.6, 3.2 Hz), 1.33 (3H, t, J = 7.2 Hz), 1.26-1.19 (2H, m), 1.04 (9H, s), 0.99-0.93 (1H, dd, J = 14.6, 11.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8, 169.7, 136.0, 134.0, 133.8, 129.3, 127.6, 61.4, 43.3, 29.6, 29.4, 27.8, 26.1, 18.1, 14.4, 9.8.

55. Method *a* was followed. 50%, viscous liquid (1.4:1 mixture of more polar and less polar isomers).

Characteristic ^{1}H signals for the major isomer (400 MHz, $CDCl_3$): δ 3.99-3.84 (2H, m), 2.13-2.06 (1H, dd, J = 14.6, 12.4 Hz), 1.91-1.88

(1H, dd, J = 9.8, 4.6 Hz), 1.69-1.65 (1H, dd, J = 9.4, 4.7 Hz), 1.09 (9H, s), 0.97 (3H, t, J = 7.1 Hz).

Characteristic ^{1}H signals for the minor isomer (400 MHz, $CDCl_3$): δ 4.24-4.16 (1H, qd, J = 10.8, 7.1 Hz), 4.13-4.05 (1H, qd, J = 10.8, 7.1 Hz), 2.23-2.15 (1H, m), 1.82-1.75 (1H, dd, J = 8.5, 4.9 Hz), 1.48-1.40 (2H, m), 1.18 (3H, t, J = 7.1 Hz), 1.04 (9H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 165.3, 141.4, 140.3, 136.1, 136.04, 136.0, 135.8, 133.7, 133.5, 133.4, 133.3, 133.2, 129.5, 129.3, 128.8, 128.54, 128.52, 127.8, 128.74, 127.66, 62.1, 61.9, 51.0, 49.2, 32.0, 27.7, 26.8, 26.7, 24.1, 22.0, 18.14, 18.06, 14.0, 13.6, 8.71, 8.69.

56. Method *a* was followed. 73%, viscous liquid (2.4:1 mixture of more polar and less polar isomers).

56 (less polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.91 (1H, m), 7.69-7.29 (14H, m), 2.66-2.61 (1H, m), 1.60-1.50 (1H, m), 1.43-1.36 (1H, dd, J = 15.1, 9.9 Hz), 1.32-1.27 (1H, dd, J = 15.1, 3.9 Hz), 1.25-1.18 (1H, m), 1.02 (9H, s), 0.95-0.90 (1H, dt, J = 7.8, 4.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 139.0, 136.2, 136.0, 134.6, 134.5, 132.3, 129.02, 128.96, 128.4, 127.9, 127.5, 27.8, 24.8, 22.6, 18.1, 16.8, 7.5.

56 (more polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.69 (1H, m), 7.61-7.23 (14H, m), 2.31-2.27 (1H, m), 1.67-1.58 (1H, m), 1.44-1.39 (1H, dd, J = 15.0, 6.5 Hz), 1.37-1.31 (1H, m), 1.05 (9H, s), 0.78-0.73 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 137.9, 136.0, 135.9, 134.5, 134.2, 132.3, 129.11, 129.05, 128.5, 128.2, 127.8, 127.6, 27.8, 27.6, 23.4, 21.9, 18.0, 15.8.

57. Method *a* was followed. 77%, viscous liquid (1.7:1 mixture of more polar and less polar isomers).

57 (less polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.61 (4H, m), 7.41-7.32 (6H, m), 4.19-4.11 (1H, qd, J = 10.8, 7.1 Hz), 4.09-4.01 (1H, qd, J = 10.8, 7.1 Hz), 1.58-1.52 (1H, dt, J = 8.2, 5.6 Hz), 1.46-1.43 (1H, m), 1.25 (3H, t, J = 7.1 Hz), 1.29-1.18 (1H, m), 1.05 (9H, s), 0.84-0.76 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 136.1, 136.0, 134.6, 129.0, 128.9, 127.5, 127.4, 60.1, 27.8, 19.7, 18.1, 17.9, 15.8, 14.3, 7.9.

57 (more polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.39 (4H, m), 7.39-7.31 (6H, m), 4.03-3.87 (2H, m), 1.38-1.30 (1H, m), 1.25-1.18 (1H, m), 1.15 (3H, t, J = 7.1 Hz), 1.22-1.08 (1H, m), 1.05 (9H, s), 1.07-0.95 (1H, m), 0.54-0.47 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 135.91, 135.87, 134.4, 134.3, 129.01, 129.0, 127.5, 127.47, 60.0, 27.7, 22.9, 18.7, 18.0, 17.9, 15.2, 14.1.

58. Method *b* was followed. 65%, viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s), 3.72 (3H, s), 2.00-1.92 (1H, m), 1.51-1.48 (1H, dd, J = 8.9, 4.5 Hz), 1.46-1.43 (1H, dd, J = 7.8, 4.6 Hz), 1.12-1.03 (22H, m), 0.26-0.20 (1H, dd, J = 14.6, 12.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 168.5, 52.4, 52.3, 35.9, 26.2, 23.9, 18.7, 18.6, 17.7, 12.3, 10.9, 8.4.

59. Method *b* was followed. 61%, viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.49 (2H, m), 7.36-7.34 (3H, m), 3.74 (3H, s), 3.69 (3H, s), 1.94-1.86 (1H, m), 1.44-1.41 (1H, dd, J = 8.8, 4.6 Hz), 1.30-1.27 (1H, dd, J = 7.8, 4.6 Hz), 1.22-1.17 (1H, dd, J = 14.4, 3.4 Hz), 0.43-0.36 (1H, dd, J = 14.4, 11.5 Hz), 0.34 (3H, s), 0.33 (3H, s). ^{13}C

NMR (100 MHz, $CDCl_3$): δ 170.8, 168.6, 138.0, 133.5, 129.1, 127.8, 52.43, 52.41, 34.6, 25.6, 22.8, 15.2, -3.1, -3.3.

60. Method *a* was followed. 47%, viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.86 (2H, m), 7.54-7.29 (8H, m), 2.36-2.32 (1H, m), 1.61-1.55 (1H, m), 1.53-1.49 (1H, m), 1.16-1.11 (1H, dd, J = 14.6, 6.1 Hz), 0.87-0.82 (1H, m), 0.83-0.78 (1H, dd, J = 14.6, 8.0 Hz), 0.32 (3H, s), 0.31 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 138.6, 138.0, 133.4, 132.5, 129.0, 128.4, 127.9, 127.8, 27.2, 23.4, 21.0, 20.9, -2.8, -3.2.

61. Method *a* was followed. 35%, liquid (1.2: 1 mixture of isomers). Characteristic ^{1}H signals for the major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75-2.70 (1H, m), 1.28-1.24 (1H, m), 0.00 (9H, s). Characteristic ^{1}H signals for the minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ2.40-2.37 (1H, m), 1.17-1.12 (1H, m), 0.03 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 198.8, 139.1, 138.1, 132.5, 132.4, 128.42, 128.40, 128.0, 127.9, 27.4, 24.1, 23.9, 22.3, 21.7, 21.0, 15.3, 13.5, -1.51, -1.54.

62. Method *b* was followed. 47%, viscous liquid (2:1 mixture of more polar and less polar isomers).

62. (less polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.61 (4H, m), 7.39-7.33 (6H, m), 4.21-4.04 (2H, m), 4.09 (2H, q, J = 7.1 Hz), 2.67 (1H, d, J = 17.1 Hz), 2.01 (1H, d, J = 17.1 Hz), 1.54-1.50 (1H, dd, J = 15.1, 3.6 Hz), 1.44-1.38 (1H, dd, J = 15.1, 9.3 Hz), 1.34-1.10 (2H, m), 1.24 (3H, t, J = 7.1 Hz), 1.21 (3H, t, J = 7.1 Hz), 1.04 (9H, s), 0.69-0.66 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 171.8, 136.1, 136.0,

134.5, 134.4, 129.0, 127.6, 60.6, 60.3, 40.3, 27.8, 26.8, 25.5, 22.1, 18.1, 14.3, 14.2, 8.3.

62 (more polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.59 (4H, m), 7.40-7.33 (6H, m), 4.20-3.96 (4H, m), 2.60 (1H, d, J = 17.4 Hz), 2.50 (1H, d, J = 17.1 Hz), 1.67-1.61 (1H, m), 1.34-1.20 (2H, m), 1.26 (3H, t, J = 7.1 Hz), 1.21 (3H, t, J = 7.1 Hz), 1.06 (9H, s), 0.81-0.75 (1H, dd, J = 14.4, 10.5 Hz), 0.32-0.30 (1H, dd, J = 6.8, 4.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 172.1, 136.0, 135.9, 134.3, 134.1, 127.6, 127.5, 60.5, 60.4, 34.1, 27.8, 25.4, 23.9, 23.0, 18.1, 14.2, 14.0, 10.9.

63. Method *b* was followed. 37%, viscous liquid (2.2:1 mixture of more polar and less polar isomers).

63 (less polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.59 (4H, m), 7.39-7.34 (6H, m), 4.22-4.05 (2H, m), 4.05 (2H, q, J = 7.1 Hz), 2.31 (1H, d, J = 9.0 Hz), 2.29 (1H, d, J = 8.0 Hz), 2.15-2.08 (1H, m), 1.47-1.42 (1H, dd, J = 15.3, 3.8 Hz), 1.36-1.19 (3H, m), 1.27 (3H, t, J = 7.1 Hz), 1.20 (3H, t, J = 7.1 Hz), 1.04-0.99 (1H, m), 1.03 (9H, s), 0.62 (1H, q, J = 4.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 173.0, 136.1, 136.0, 134.49, 134.48, 129.1, 127.6, 127.5, 60.5, 60.2, 32.5, 30.8, 30.0, 27.8, 25.7, 22.0, 18.1, 14.4, 14.2, 8.6.

63 (more polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.58 (4H, m), 7.39-7.33 (6H, m), 4.12 (2H, q, J = 7.1 Hz), 4.07-3.93 (2H, m), 2.61-2.53 (1H, ddd, J = 15.8, 10.7, 5.1 Hz), 2.42-2.34 (1H, ddd, J = 15.9, 10.3, 5.6 Hz), 2.11-2.04 (1H, ddd, J = 14.4, 10.2, 5.1 Hz), 1.69-1.61 (1H, ddd, J = 14.4, 10.5, 5.1 Hz), 1.59-1.54 (1H, dd, J = 14.7, 3.3 Hz), 1.52-1.45 (1H, m), 1.26 (3H, t, J = 7.1 Hz), 1.22-1.14 (1H, m), 1.13

(3H, t, J = 7.1 Hz), 1.06 (9H, s), 0.98-0.91 (1H, dd, J = 14.6, 10.6 Hz), 0.21-0.18 (1H, dd, J = 6.6, 4.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 173.8, 136.05, 135.97, 134.4, 134.3, 129.1, 127.6, 127.5, 60.3, 32.7, 27.9, 27.8, 24.4, 23.9, 23.0, 18.2, 14.2, 14.1, 10.4.

64. Method *b* was followed. 34%, viscous liquid (1.8:1 mixture of more polar and less polar isomers).

64 (less polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.59 (4H, m), 7.42-7.33 (6H, m), 4.08 (2H, q, J = 7.1 Hz), 2.96 (1H, d, J = 17.1 Hz), 2.06 (3H, s), 1.99 (1H, d, J = 17.1 Hz), 1.32-1.12 (4H, m), 1.19 (3H, t, J = 7.1 Hz), 1.02 (9H, s), 0.65-0.62 (1H, dd, J = 8.3, 4.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5, 171.7, 136.1, 136.0, 134.5, 134.3, 129.1, 127.6, 127.5, 60.7, 41.4, 34.4, 28.8, 28.4, 27.8, 21.9, 18.1, 14.1, 7.9.

64 (more polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.59 (4H, m), 7.41-7.34 (6H, m), 4.15 (2H, q, J = 7.1 Hz), 2.68 (1H, d, J = 17.3 Hz), 2.52 (1H, d, J = 17.1 Hz), 1.78 (3H, s), 1.65-1.61 (1H, m), 1.58-1.49 (1H, m), 1.36-1.33 (1H, dd, J = 9.0, 5.1 Hz), 1.26 (3H, t, J = 7.1 Hz), 1.06 (9H, s), 0.89-0.83 (1H, dd, J = 14.6, 10.2 Hz), 0.44 (1H, t, J = 5.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 172.2, 136.0, 135.9, 134.1, 134.0, 129.3, 127.8, 127.7, 60.5, 34.6, 34.3, 27.8, 24.3, 24.2, 23.7, 18.2, 14.2, 10.8.

$TiCl_4$-promoted dihydrofuran formation

Typical procedure for the conversion of 52 into 81

To a solution of **52** (0.102 g, 0.25 mmol) in dry CH_2Cl_2 (1.5 mL), a solution of $TiCl_4$ (0.057 g, 0.3 mmol) in dry CH_2Cl_2 (1.5 mL) was added at –30 °C. The reaction mixture was stirred for 3 h and then

quenched with saturated aq NH_4Cl solution. Et_2O (10 mL) was added to it and the layers were separated. The aq layer was extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with water and brine, and dried. Removal of the solvents furnished the crude product that was purified by column chromatography (EtOAc/hexanes) to isolate **81**, 98 mg, 96%, colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.62 (4H, m), 7.44-7.35 (6H, m), 4.07-3.99 (1H, m), 3.64 (3H, s), 3.51 (3H, s), 2.17-2.01 (2H, m), 2.05-2.00 (1H, dd, J = 15.1, 6.1 Hz), 1.84-1.77 (1H, dd, J = 15.1, 8.3 Hz), 1.03 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 168.8, 136.2, 136.1, 133.4, 133.0, 129.5, 129.4, 127.71, 127.69, 59.6, 52.4, 49.7, 39.9, 27.7, 23.1, 18.2. Anal. Calcd. for $C_{24}H_{30}O_4Si$: C, 70.21; H, 7.36. Found C, 70.09; H, 7.20.

82. 81%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.62 (4H, m), 7.44-7.34 (6H, m), 4.72-4.64 (1H, m), 2.56-2.50 (1H, ddd, J = 14.2, 9.8, 1.4 Hz), 2.28-2.22 (1H, ddd, J = 15.6, 7.8, 1.5 Hz), 2.06 (3H, s), 1.97 (3H, s), 1.90-1.85 (1H, dd, J = 14.5, 5.5 Hz), 1.61-1.55 (1H, dd, J = 14.4, 9.0 Hz), 1.06 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 167.3, 136.1, 136.0, 134.0, 133.7, 129.4, 129.3, 127.72, 127.69, 111.7, 81.3, 38.2, 29.2, 27.7, 19.3, 18.1, 14.9. Anal. Calcd. for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99. Found C, 76.01; H, 7.84.

83. 70%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.61 (4H, m), 7.43-7.34 (6H, m), 4.70-4.61 (1H, m), 4.08 (2H, q, J = 7.1 Hz), 2.56-2.50 (1H, dd, J = 14.4, 9.8 Hz), 2.27-2.22 (1H, dd, J = 14.5, 7.7 Hz), 2.03 (3H, s), 1.89-1.84 (1H, dd, J = 14.4, 5.8 Hz), 1.60-

1.54 (1H, dd, J = 14.5, 8.7 Hz), 1.20 (3H, t, J = 7.2 Hz), 1.05 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 166.3, 136.1, 136.0, 134.0, 133.9, 129.3, 129.2, 127.64, 127.59, 101.6, 81.0, 59.2, 37.6, 27.7, 19.4, 18.0, 14.4, 14.1. Anal. Calcd. for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found C, 73.31; H, 7.76.

84. 75%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.32 (15H, m), 4.12-4.00 (1H, m), 3.95-3.80 (2H, m), 2.26-2.13 (2H, m), 2.05-1.99 (1H, dd, J = 15.0, 6.2 Hz), 1.85-1.79 (1H, dd, J = 15.0, 8.4 Hz), 0.99 (9H, s), 0.98 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 136.9, 136.03, 136.0, 134.0, 133.1, 132.5, 129.6, 129.4, 129.23, 129.17, 128.9, 128.6, 127.9, 127.8, 127.7, 68.9, 58.4, 37.7, 27.6, 23.1, 18.1, 13.7. Anal. Calcd. for $C_{29}H_{34}O_4SSi$: C, 68.74; H, 6.76. Found C, 68.61; H, 6.60.

85. 45%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.87 (2H, m), 7.68-7.62 (4H, m), 7.52 (1H, t, J = 7.3 Hz), 7.43-7.35 (8H, m), 3.90-3.82 (1H, m), 3.06-2.87 (2H, m), 1.91-1.77 (2H, m), 1.59-1.49 (2H, m), 1.04 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 136.1, 136.0, 134.3, 134.2, 129.44, 129.36, 128.5, 128.1, 127.9, 127.8, 127.6, 68.9, 35.1, 34.8, 27.8, 20.6, 18.1. Anal. Calcd. for $C_{27}H_{32}O_2Si$: C, 77.84; H, 7.74. Found C, 77.67; H, 7.56.

86. 54%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (1H, t, J = 8.0 Hz), 3.82 (3H, s), 3.78 (3H, s), 2.34-2.28 (2H, m), 1.04 (9H, s), 0.75-0.71 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 164.6, 152.9, 52.3, 52.2, 24.9, 18.7, 10.8, 8.3. Anal. Calcd. for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found C, 61.95; H, 9.72.

$HClO_4$-assisted hydrolysis of 81

A solution of **81** (0.08 g, 0.2 mmol) in 10% $HClO_4$ in THF (2 mL) was refluxed for 5 h. The reaction mixture was cooled and taken in Et_2O (15 mL). It was washed with water (2 x 10 mL) and brine (1 x 10 mL). The organic layer was dried and concentrated under reduced pressure. Column chromatography of the crude material over silica gel (EtOAc/hexanes) furnished 1:1.8 diastereomeric mixture of pure 3-carbomethoxy-5-*tert*-butyldiphenylsilylmethyl-γ-lactone **88**, 0.065 g, 84%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.58 (m), 7.43-7.34 (m), 4.82-4.74 (m), 4.51-4.44 (m), 3.72 (s), 3.65 (s), 3.44-3.40 (dd, J = 9.6, 4.6 Hz), 3.39-3.33 (dd, J = 11.4, 8.9 Hz), 2.09-1.95 (m), 1.88-1.81 (m), 1.71-1.64 (m), 1.64-1.58 (dd, J = 14.6, 10.2 Hz), 1.52-1.45 (dd, J = 14.4, 10.5 Hz), 1.05 (s), 1.04 (s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 168.2, 168.0, 135.9, 135.8, 133.6, 133.4, 132.6, 129.6, 127.9, 127.8, 79.6, 78.8, 52.84, 52.81, 47.9, 47.3, 34.5, 34.1, 27.6, 27.5, 18.5, 18.1, 18.0.

Characteristic ^{1}H signals for the major isomer. δ 4.51-4.44 (1H, m), 3.72 (3H, s), 3.39-3.33 (1H, dd, J = 11.4, 8.9 Hz), 1.64-1.58 (1H, dd, J = 14.6, 10.2 Hz), 1.04 (9H, s).

Characteristic ^{1}H signals for the minor isomer. δ 4.82-4.72 (1H, m), 3.65 (3H, s), 3.44-3.40 (1H, dd, J = 9.6, 4.6 Hz), 1.52-1.45 (1H, dd, J = 14.4, 10.5 Hz), 1.05 (9H, s).

89. The above procedure was followed to obtain a 1:1.3 diastereomeric mixture of 3-phenylsulfonyl-5-*tert*-butyldiphenylsilylmethyl-γ-lactone **89** from **84** in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.37 (m),

4.78-4.70 (m), 4.51-4.44 (m), 3.96 (t, J = 9.7 Hz), 3.85-3.82 (dd, J = 10.0, 2.4 Hz), 2.36-2.30 (ddd, J = 14.8, 6.1, 2.7 Hz), 2.22-2.14 (ddd, J = 14.2, 9.5, 8.0 Hz), 2.11-2.01 (m), 1.89-1.81 (m), 1.66-1.60 (m), 1.49-1.43 (dd, J = 14.4, 10.8 Hz), 1.05 (s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 166.9, 137.0, 136.7, 136.0, 135.91, 135.87, 134.6, 134.5, 133.5, 133.2, 132.5, 132.4, 129.8, 129.7, 129.5, 129.2, 129.1, 128.1, 128.0, 79.7, 77.8, 65.9, 64.7, 32.4, 31.2, 27.6, 27.5, 19.0, 18.4, 18.1.

Characteristic ^{1}H signals for the major isomer. δ 4.78-4.70 (1H, m), 3.85-3.82 (1H, dd, J = 10.0, 2.4 Hz), 2.36-2.30 (1H, ddd, J = 14.8, 6.1, 2.7 Hz), 1.49-1.43 (1H, dd, J = 14.4, 10.8 Hz).

Characteristic ^{1}H signals for the minor isomer. δ 4.51-4.44 (1H, m), 3.96 (1H, t, J = 9.7 Hz), 2.22-2.14 (1H, ddd, J = 14.2, 9.5, 8.0 Hz), 1.66-1.60 (1H, m).

Dealkyldecarboxylation of 3-carbomethoxy-5-*tert*-butyldiphenylsilylmethyl-γ-lactone 88

To a solution of 3-carbomethoxy-5-*tert*-butyldiphenylsilylmethyl-γ-lactone **88** (0.022 g, 0.056 mmol) in DMSO (0.5 mL), NaCl (0.007 g, 0.112 mmol) and a droplet of water were added. After refluxing for 4 h (oil bath temperature 160-180 °C), the mixture was cooled to 25 °C and taken in Et_2O (10 mL). This was washed with water (2 x 5 mL) and brine (1 x 5 mL). Solvent removal and purification of the residue through silica gel column chromatography (EtOAc/hexanes) furnished pure 5-*tert*-butyldiphenylsilylmethyl-γ-lactone **90**, 0.016 g, 85%, solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.71 (4H, m), 7.45-7.35 (6H, m), 4.60-4.53

(1H, m), 2.40-2.23 (2H, m), 2.06-2.01 (1H, dd, J = 14.4, 3.9 Hz), 1.69-1.41 (3H, m), 1.05 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 136.0, 135.9, 133.9, 132.9, 129.62, 129.58, 127.9, 127.8, 80.1, 30.6, 29.6, 27.6, 18.5, 18.1. ν_{max} (film) 2934, 1765, 1174 cm^{-1}. Anal. Calcd. for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found C, 74.43; H, 7.64.

Desulfonation of 3-phenylsulfonyl-5-*tert*-butyldiphenylsilylmethyl-γ-lactone 89

To a solution of 3-phenylsulfonyl-5-*tert*-butyldiphenylsilylmethyl-γ-lactone **89** (0.042 g, 0.09 mmol) and anhydrous disodium hydrogen phosphate (0.05 g, 0.35 mmol) in methanol (1 mL) was added pulverized 5% sodium amalgum (0.262 g). The reaction mixture was stirred for 4 h and then poured into water (10 mL). The products were extracted into Et_2O and the etheral solution was washed with brine, dried, and concentrated. Purification of the residue using silica gel column chromatography (EtOAc/hexanes) furnished pure 5-*tert*-butyldiphenylsilylmethyl-γ-lactone **90**, 0.022 g, 74%.

92. To a solution of allyl-*tert*-butyldiphenylsilane (0.816 g, 2.9 mmol) and 2-diazocyclohexan-1,3-dione **51e** in anhydrous $CHCl_3$ (2 mL), rhodium(II)acetate dimer (0.014 g, 2 mol%) was added. After refluxing for 5 h, the reaction mixture was concentrated and the residue, thus obtained, was chromatographed over silica gel (EtOAc/hexanes) to furnish pure **92**, 0.091 g, 15% (overall), 95% (based on the reacted allyl-*tert*-butyldiphenylsilane), colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.60 (4H, m), 7.43-7.34 (6H, m), 4.86-4.78 (1H,

m), 2.55-2.49 (1H, dd, J = 14.5, 9.6 Hz), 2.28-2.20 (5H, m), 1.97-1.89 (3H, m), 1.67-1.61 (1H, dd, J = 14.4, 9.0 Hz), 1.05 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 177.0, 135.99, 135.97, 133.7, 133.5, 129.5, 129.4, 127.8, 127.7, 113.0, 85.0, 36.3, 33.9, 27.7, 23.9, 21.6, 19.4, 18.1. Anal. Calcd. for $C_{25}H_{30}O_2Si$: C, 76.88; H, 7.74. Found C, 76.70; H, 7.62.

Typical procedure for the formation of tetrahydrofuran derivative 100 from 56 and butyraldehyde

To a stirred solution of **56** (0.103 g, 0.26 mmol) and butyraldehyde (0.024 g, 0.34 mmol) in anhydrous CH_2Cl_2 (0.8 mL) at –78 °C, a solution of $TiCl_4$ (0.059 g, 0.31 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added slowly under nitrogen atmosphere. The reaction mixture turned deep red. After stirring for 2 h at –78 °C, it was warmed slowly to –30 °C. Stirring was continued at this temperature for 5 h and the reaction mixture was taken in Et_2O (20 mL). The etheral layer was washed with saturated aq NH_4Cl (2 x 10 mL) and water (10 mL). The combined aq washings were extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine, dried, and concentrated. Purification of the crude residue by silica gel column (EtOAc/hexanes) gave pure **100**, 0.044 g, 36% and **85**, 0.021 g, 21%.

100 (major isomer). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.26 (15H, m), 4.36-4.31 (1H, dt, J = 7.3, 4.2 Hz), 4.22-4.15 (1H, m), 3.51-3.44 (1H, m), 1.88-1.83 (1H, dd, J = 14.6, 4.8 Hz), 1.81-1.74 (1H, m), 1.59-1.44 (3H, m), 1.42-1.27 (1H, m), 1.24-1.05 (2H, m), 1.03 (9H, s), 0.83 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 136.7,

136.2, 137.1, 134.6, 134.0, 133.1, 129.1, 128.6, 128.3, 127.6, 127.5, 79.9, 76.6, 53.2, 40.2, 37.5, 27.7, 20.7, 19.4, 18.14, 18.09, 14.0. Anal. Calcd. for $C_{31}H_{38}O_2Si$: C, 79.10; H, 8.14. Found C, 78.96; H, 8.01.

101 (major isomer). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79-7.26 (15H, m), 5.83- 5.74 (1H, m), 5.14 (1H, d, J = 17.1 Hz), 5.03 (1H, d, J = 10.2 Hz), 4.72 (1H, t, J = 6.8 Hz), 4.29-4.22 (1H, m), 3.64-3.58 (1H, m), 1.94-1.90 (1H, dd, J = 14.6, 4.2 Hz), 1.76-1.69 (1H, m), 1.65-1.52 (2H, m), 1.03 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 137.6, 136.6, 136.12, 136.06, 134.5, 133.8, 133.2, 129.2, 128.5, 128.4, 127.6, 127.5, 116.0, 81.0, 77.5, 53.4, 39.5, 27.7, 18.2, 18.1. Anal. Calcd. for $C_{30}H_{34}O_2Si$: C, 79.25; H, 7.54. Found C, 79.15; H, 7.40.

103 (less polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (1H, d, J = 7.4 Hz), 7.57-7.29 (14H, m), 3.91-3.87 (1H, dd, J = 11.1, 2.5 Hz), 3.65-3.57 (1H, m), 2.16-2.09 (1H, m), 1.98-1.93 (1H, dd, J = 14.9, 6.1 Hz), 1.95-1.88 (1H, m), 1.78-1.72 (1H, dd, J = 14.9, 8.2 Hz), 1.60-1.50 (1H, m), 1.41-1.26 (2H, m), 1.17-1.00 (2H, m), 0.97 (9H, s), 0.82 (3H, t, J = 7.6 Hz), 0.72 (3H, t, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 138.6, 136.1, 136.0, 133.6, 133.3, 133.0, 129.4, 129.2, 128.6, 128.5, 127.61, 127.56, 76.6, 61.3, 47.6, 40.9, 30.3, 27.7, 26.5, 23.9, 18.1, 7.7, 7.4. Anal. Calcd. for $C_{32}H_{42}O_3Si$: C, 76.45; H, 8.42. Found C, 76.25; H, 8.27.

103 (more polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-7.96 (1H, m), 7.62-7.35 (14H, m), 4.04-3.98 (1H, m), 3.70-3.67 (1H, dd, J = 7.1, 3.9 Hz), 2.22-2.16 (1H, td, J = 15.1, 3.9 Hz), 2.13-2.05 (1H, ddd, J = 15.4, 9.3, 7.1 Hz), 1.90-1.84 (1H, dd, J = 15.1, 6.8 Hz), 1.75-1.70 (1H, dd, J

= 15.2, 7.3 Hz), 1.31-1.21 (2H, m), 1.12-1.04 (2H, m), 0.95 (9H, s), 0.67 (3H, t, J = 7.3 Hz), 0.61 (3H, t, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.1, 138.0, 136.2, 136.1, 133.4, 133.2, 133.1, 129.5, 129.3, 128.8, 128.6, 127.7, 127.6, 62.3, 47.8, 40.5, 30.1, 27.6, 26.7, 22.9, 18.1, 7.8, 7.5. Anal. Calcd. for $C_{32}H_{42}O_3Si$: C, 76.45; H, 8.42. Found C, 76.33; H, 8.31.

105 (less polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.81 (1H, m), 7.54-7.25 (14H, m), 3.83-3.79 (1H, dd, J = 10.8, 2.5 Hz), 3.68-3.61 (1H, m), 2.15-2.08 (1H, ddd, J = 14.6, 11.0, 2.0 Hz), 2.01-1.95 (1H, m), 1.99-1.94 (1H, dd, J = 14.9, 5.9 Hz), 1.77-1.71 (1H, dd, J = 15.0, 8.2 Hz), 1.67-1.42 (4H, m), 1.32-1.02 (6H, m), 0.97 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.2, 138.3, 136.1, 136.0, 133.5, 133.4, 133.1, 129.3, 129.2, 128.54, 128.48, 127.6, 127.5, 73.1, 61.3, 50.8, 40.6, 37.4, 35.1, 27.6, 25.5, 23.7, 21.8, 21.7, 18.1. Anal. Calcd. for $C_{33}H_{42}O_3Si$: C, 77.00; H, 8.22. Found C, 76.90; H, 8.11.

105 (more polar). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-7.96 (1H, m), 7.64-7.32 (14H, m), 4.09-4.01 (1H, m), 3.53-3.50 (1H, dd, J = 6.8, 3.9 Hz), 2.2-1.69 (4H, m), 1.93-1.88 (1H, dd, J = 15.1, 6.1 Hz), 1.77-1.71 (1H, dd, J = 15.1, 8.1 Hz), 1.52-1.32 (2H, m), 1.31-1.18 (2H, m), 1.15-0.98 (3H, m), 0.96 (9H, s), 0.89-0,78 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 138.1, 136.2, 136.1, 136.0, 134.8, 133.4, 133.3, 133.1, 129.5, 129.4, 128.8, 128.6, 127.8, 127.7, 73.4, 62.8, 52.2, 40.2, 36.6, 35.0, 27.6, 27.5, 25.4, 23.0, 21.6, 18.2. Anal. Calcd. for $C_{33}H_{42}O_3Si$: C, 77.00; H, 8.22. Found C, 76.84; H, 8.09.

107. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.93 (2H, m), 7.59-7.46 (3H, m), 5.81-5.71 (1H, tdd, J = 17.1, 10.0, 7.1 Hz), 5.06-5.00 (1H, qd, J = 16.8, 1.5 Hz), 4.93 (1H, d, J = 10.0 Hz), 3.98-3.94 (1H, m), 3.62-3.58 (1H, m), 2.65-2.52 (2H, m), 1.60-1.32 (4H, m), 0.91 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 137.2, 135.9, 133.4, 128.7, 128.5, 116.8, 71.7, 50.6, 37.1, 31.8, 19.3, 13.9. ν_{max} (film) 3446, 2962, 1676, 1450 cm^{-1}. Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found C, 77.46; H, 8.55.

108. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.93 (2H, m), 7.60-7.47 (3H, m), 5.81-5.71 (1H, tdd, J = 17.1, 10.0, 7.1 Hz), 5.11-5.05 (1H, qd, J = 17.1, 1.5 Hz), 5.00 (1H, d, J = 10.0 Hz), 3.91-3.87 (1H, m), 3.61-3,56 (1H, dt, J = 6.8, 4.6 Hz), 2.54 (2H, t, J = 7.1 Hz), 1.60-1.32 (4H, m), 0.89 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 137.5, 134.9, 133.5, 128.8, 128.3, 117.4, 72.3, 50.2, 37.9, 34.5, 19.2, 13.9. ν_{max} (film) 3449, 2955, 1680, cm^{-1}. Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found C, 77.38; H, 8.50.

Conversion of 100 into 106 *via* oxidative cleavage of carbon-silicon bond

Boron trifluoride/acetic acid complex (BF_3•2AcOH) (0.14 mL, 1 mmol) was added to a solution of **100** (0.047 g, 0.1 mmol) in dry CH_2Cl_2 (2 mL). The reaction mixture was heated at reflux for 7 h. The reaction mixture was then cooled to rt and poured into aq $NaHCO_3$. The aq layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried and concentrated to obtain a residue.

The above residue was dissolved in THF (1 mL)/methanol (1 mL) and $NaHCO_3$ (0.008 g, 0.1 mmol), KF (0.017 g, 0.3 mmol), and H_2O_2 (0.1 mL, 1 mmol, 30%) were added successively. The reaction mixture was stirred for 5 h at rt and then refluxed for 3 h. It was cooled to rt and taken in Et_2O (15 mL). The etheral layer was washed with water (2 x 5 mL) and the combined aq washings were extracted with Et_2O (2 x 5 mL). The combined organic extracts were dried and concentrated. Chromatographic purification of the residue furnished pure **106**, 0.025 g, 45%, colorless viscous liquid.

106a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.95 (2H, m), 7.60-7.47 (3H, m), 4.39-4.34 (1H, m), 4.32-4.26 (1H, dq, J = 7.6, 3.4 Hz), 3.79-3.73 (1H, dt, J = 8.6, 6.8 Hz), 3.71-3.67 (1H, dd, J = 11.7, 3.3 Hz), 3.66-3.61 (1H, dd, J = 11.7, 6.1 Hz), 2.41-2.34 (1H, ddd, J = 12.4, 8.6, 7.1 Hz), 2.08-2.00 (1H, td, J = 12.7, 8.2 Hz), 1.68-1.58 (1H, m), 1.56-1.42 (2H, m), 1.36-1.28 (1H, m), 0.90 (3H, t, J = 7.1 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ 199.9, 136.6, 133.4, 128.8, 128.4, 81.2, 78.9, 64.6, 51.9, 37.0, 33.0, 29.7, 19.4, 14.0. Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found C, 72.38; H, 8.00.

Conversion of β-hydroxy ketone 107 into tetrahydrofuran derivatives 106a and 106b[25]

To a stirred solution of **107** (0.014 g, 0.06 mmol) in anhydrous benzene (1 mL), *m*-CPBA (0.016 g, 0.09 mmol) was added in portions at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and then warmed to room temperature. After stirring for 19 h at room temperature, the reaction mixture was quenched with saturated aq

Na_2SO_3 solution (4 mL). Et_2O (10 mL) was added and the layers were separated. The etheral solution was washed with saturated aq $NaHCO_3$ solution (2 x 5mL). The combined aq washings were extracted with Et_2O (2 x5 mL). The combined organic extracts were washed with brine, dried, and concentrated to obtain the crude product. This was purified by silica gel column chromatography (EtOAc/hexanes) to furnish a mixture of **106a** and **106b**, 0.0091 g, 61%. Separation of **106a** from **106b** was achieved by radial chromatography.

106b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.95 (2H, m), 7.60-7.47 (3H, m), 4.32-4.27 (1H, dt, J = 7.6, 4.6 Hz), 4.22-4.16 (1H, m), 3.83-3.80 (1H, dd, J = 11.7, 3.0 Hz), 3.69-3.63 (1H, dt, J = 9.8, 7.3 Hz), 3.57-3.53 (1H, dd, J = 11.8, 4.5 Hz), 2.27-2.20 (1H, ddd, J = 12.4, 10.0, 7.3 Hz), 2.19-2.12 (1H, td, J = 12.4, 7.3 Hz), 1.68-1.30 (4H, m), 0.90 (3H, t, J = 7.13 Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ 200.4, 136.7, 133.4, 128.8, 128.4, 82.1, 78.8, 64.3, 51.6, 37.2, 33.1, 19.4, 14.1. Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found C, 72.44; H, 8.04.

General procedure for the $LiAlH_4$ reduction of diesters 52, 62, and 63 into diols 128, 129, and 130

To a stirred solution of the diester (0.25 mmol) in anhydrous Et_2O (2 mL) at 0 °C, $LiAlH_4$ (0.75 mmol) was added in portions under nitrogen atmosphere. The reaction mixture was stirred for 5 h at rt and Et_2O (10 mL) was added to it. It was quenched with drops of EtOAc and water. The etheral solution was dried and filtered through a celite pad. Concentration of the organic solution and purification by chromatography (EtOAc/hexanes) furnished the corresponding diol.

128. 92%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.61 (4H, m), 7.39- 7.33 (6H, m), 3.75 (1H, d, J = 14.4 Hz), 3.56 (1H, d, J = 11.7 Hz), 3.30 (2H, s), 1.53-1.48 (1H, dd, J = 15.1, 4.6 Hz), 1.10-1.04 (1H, dd, J = 15.2, 8.6 Hz), 1.05 (9H, s), 0.82-0.76 (1H, m), 0.45-0.42 (1H, dd, J = 8.6, 4.9 Hz), 0.04 (1H, t, J = 5.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.04, 135.98, 134.6, 134.4, 129.2, 129.1, 127.6, 127.5, 70.6, 65.3, 28.4, 27.8, 18.1, 17.8, 17.3, 9.6.

129a. 94%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.61 (4H, m), 7.39- 7.33 (6H, m), 3.75 (1H, d, J = 14.4 Hz), 3.56 (1H, d, J = 11.7 Hz), 3.30 (2H, s), 1.53-1.48 (1H, dd, J = 15.1, 4.6 Hz), 1.10-1.04 (1H, dd, J = 15.2, 8.6 Hz), 1.05 (9H, s), 0.82-0.76 (1H, m), 0.45-0.42 (1H, dd, J = 8.6, 4.9 Hz), 0.04 (1H, t, J = 5.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.04, 135.98, 134.6, 134.4, 129.2, 129.1, 127.6, 127.5, 70.6, 65.3, 28.4, 27.8, 18.1, 17.8, 17.3, 9.6.

129b. 91%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.59 (4H, m), 7.40-7.33 (6H, m), 3.76-3.71 (1H, ddd, J = 10.8, 6.3, 4.4 Hz), 3.66-3.61 (1H, ddd, J = 10.8, 7.8, 3.9 Hz), 3.23 (1H, d, J = 11.4 Hz), 3.04 (1H, d, J = 11.2 Hz), 1.70-1.63 (1H, ddd, J = 14.9, 8.0, 4.2 Hz), 1.55-1.49 (1H, ddd, J = 15.0, 6.2, 3.9 Hz), 1.41-1.36 (1H, dd, J = 15.0, 4.2 Hz), 1.05 (9H, s), 0.97-0.89 (1H, dd, J = 15.0, 8.6 Hz), 0.73-0.66 (1H, m), 0.49-0.46 (1H, dd, J = 8.5, 4.9 Hz), -0.10 (1H, t, J = 5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 134.8, 134.6, 129.1, 127.5, 71.6, 61.5, 34.0, 27.9, 26.1, 18.7, 18.4, 18.1, 9.9.

130a. 98%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.61 (4H, m), 7.40-7.33 (6H, m), 3.64 (1H, d, J = 11.7 Hz), 3.51

(2H, t, J = 6.2 Hz), 3.45 (1H, d, J = 11.7 Hz), 1.57-1.36 (4H, m), 1.50-1.45 (1H, dd, J = 14.9, 4.1 Hz), 1.07-1.04 (1H, m), 1.05 (9H, s), 0.71-0.66 (1H, m), 0.37-0.34 (1H, dd, J = 8.4, 4.7 Hz), -0.04 (1H, t, J = 5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 136.0, 134.9, 134.6, 129.2, 129.1, 127.6, 127.5, 64.4, 62.9, 32.0, 29.3, 27.9, 26.4, 19.5, 19.4, 18.1, 10.2.

130b. 93%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.60 (4H, m), 7.41-7.34 (6H, m), 3.66 (2H, t, J = 6.1 Hz), 3.31 (1H, d, J = 11.5 Hz), 2.98 (1H, d, J = 11.2 Hz), 1.77-1.45 (4H, m), 1.43-1.38 (1H, dd, J = 15.1, 4.6 Hz), 1.07-1.04 (1H, m), 1.05 (9H, s), 0.67-0.59 (1H, m), 0.40-0.37 (1H, dd, J = 8.8, 4.6 Hz), -0.11 (1H, t, J = 5.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 136.0, 135.0, 134.6, 129.2, 129.1, 127.62, 127.56, 69.7, 63.1, 29.9, 27.9, 26.6, 25.0, 18.6, 18.18, 18.16, 9.3.

$NaBH_4$ reduction of 54

To a solution of **54** (more polar isomer, 0.056 g, 0.138 mmol) in methanol (2 mL), $NaBH_4$ (0.006 g, 0.16 mmol) was added at 0 °C. It was stirred for 30 min and concentrated. Et_2O (15 mL) was added to the residue and the etheral solution was washed with saturated aq NH_4Cl (2 x 5 mL). The combined aq washings were extracted with Et_2O (2 x 5 mL). The combined organic extracts were dried and concentrated. Purification of the crude product by silica gel chromatography furnished 1.6:1 mixture of the diastereomeric alcohols **131b**, 0.05 g, 89%, colorless viscous liquid. Characteristic ^{1}H signals for the major isomer: (400 MHz, $CDCl_3$): δ 2.97 ($H_3CC\mathit{H}$-OH, q, J =

6.4 Hz), 1.31 (H_3CCHOH, d, J = 7.6 Hz), 1.03 (C(CH_3)$_3$). Characteristic ^{1}H signals for the minor isomer: (400 MHz, $CDCl_3$): δ 2.97 (H_3CCH-OH, q, J = 6.4 Hz), 1.16 (H_3CCHOH, d, J = 6.4 Hz), 1.04 (C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 136.1, 136.02, 136.0, 134.5, 134.4, 134.2, 129.2, 129.1, 127.62, 127.60, 127.53, 127.51, 73.4, 69.4, 60.6, 60.5, 36.0, 35.7, 27.8, 24.7, 20.9, 20.8, 20.7, 20.0, 19.3, 18.1, 14.5, 14.4, 8.9, 8.5.

131a. 86%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.62 (4H, m), 7.40-7.34 (6H, m), 4.12-3.96 (2H, m), 3.48 (2H, br s), 1.99-1.94 (1H, dd, J = 14.9, 2.4 Hz), 1.48-1.40 (1H, m), 1.40 (3H, d, J = 4.9 Hz), 1.29-1.26 (1H, dd, J = 9.0, 4.6 Hz), 1.12 (3H, t, J = 7.2 Hz), 1.06 (9H, s), 1.02-0.95 (1H, dd, J = 14.9, 10.9 Hz), 0.17-0.14 (1H, dd, J = 6.8, 4.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 136.0, 134.5, 134.2, 129.1, 127.6, 127.5, 68.6, 60.3, 33.1, 27.8, 25.5, 21.9, 21.6, 18.2, 14.1, 9.9.

Na(CN)BH_3 reduction of 64

A small crystal of methyl orange was added to a solution of **64** (less polar isomer, 0.025 g, 0.059 mmol) in methanol (1 mL) at 0 °C. The solution turned yellow. Drops of 2N HCl/MeOH were added so that the solution turned red. Now, Na(CN)BH_3 (0.0045 g, 0.071 mmol) was added slowly. Whenever the color of the reaction mixture started to turn to yellow during and after the addition of Na(CN)BH_3, drops of 2N HCl/MeOH were added immediately to restore the red color. After stirring for 2 h, it was concentrated. Saturated aq NH_4Cl (5 mL) was added to the residue and the products were extracted into Et_2O (2 x 10

mL). The combined organic extracts were dried and the solvents evaporated. The residue, thus left, was purified through a short column of silica gel to obtain a >15:1 mixture of the diastereomeric alcohols **132a**, 0.0225 g, 90%, colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.58 (4H, m), 7.40-7.33 (6H, m), 4.06 (2H, q, J = 7.1 Hz), 3.51 (1H, q, J = 6.3 Hz), 2.77 (1H, d, J = 16.8 Hz), 1.70 (1H, d, J = 16.8 Hz), 1.59-1.54 (1H, dd, J = 14.6, 2.2 Hz), 1.26 (3H, d, J = 6.6 Hz), 1.19 (3H, t, J = 7.1 Hz), 1.05 (9H, s), 0.90-0.84 (1H, dd, J = 14.7, 11.0 Hz), 0.74-0.71 (1H, m), 0.57-0.53 (1H, dd, J = 8.6, 5.4 Hz), 0.30 (1H, t, J = 5.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 136.1, 135.9, 134.6, 134.5, 129.1, 127.6, 127.5, 70.7, 60.8, 39.0, 29.7, 27.9, 25.9, 21.5, 20.5, 20.4, 18.1, 14.1, 10.0.

132b. 92% (1:1 mixture of diastereomeric alcohols), colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.58 (8H, m), 7.40-7.34 (12H, m), 4.25-4.11 (4H, m), 2.97-2.87 (2H, m), 2.75 (1H, d, J = 17.0 Hz), 2.72 (1H, dd, J = 16.8, 0.9 Hz), 2.23 (1H, d, J = 17.0 Hz), 2.22 (1H, d, J = 16.8 Hz), 1.68-1.64 (1H, dd, J = 14.5, 2.5 Hz), 1.48-1.44 (1H, dd, J = 14.6, 2.4 Hz), 1.29 (3H, t, J = 7.1 Hz), 1.28 (3H, t, J = 7.1 Hz), 1.06 (3H, d, J = 6.1 Hz), 1.05 (9H, s), 1.045 (9H, s), 0.99 (3H, d, J = 6.3 Hz), 0.95-0.87 (1H, m), 0.82-0.61 (4H, m), 0.40-0.36 (1H, dd, J = 8.8, 5.1 Hz), 0.11 (1H, t, J = 5.1 Hz), -0.08 (1H, t, J = 5.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 136.1, 136.0, 135.9, 135.8, 134.7, 134.6, 134.5, 134.3, 129.14, 129.08, 127.6, 127.58, 127.5, 75.3, 75.2, 60.9, 33.6, 32.8, 27.9, 27.3, 27.0, 21.1, 19.6, 19.5, 19.40, 19.37, 18.2, 18.1, 16.9, 14.18, 14.16, 10.5, 10.2.

_p_-TSA promoted conversion of cyclopropyl carbinols 128-132 into oxacycles and lactones

Typical procedure for the conversion of 128 into 133

To a solution of **128** (0.055 g, 0.155 mmol) in dry THF (1.5 mL), _p_-TSA (0.035 g, 0.186 mmol) was added. After refluxing for 3 h, the reaction mixture was taken in Et_2O (15 mL) and washed with water (2 x 5 mL). The combined aq washings were extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine and dried. Removal of solvents under reduced pressure furnished the crude product which was purified by column chromatography (EtOAc/hexanes) to isolate **133**, 0.045 g, 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.61 (4H, m), 7.42-7.33 (6H, m), 4.75 (1H, t, J = 2.2 Hz), 4.72 (1H, t, J = 2.2 Hz), 4.29 (1H, d, J = 13.2 Hz), 4.07-4.03 (1H, dd, J = 13.4, 1.4 Hz), 4.01- 3.94 (1H, m), 2.03-1.97 (1H, dd, J = 15.6, 5.6 Hz), 1.87-1.83 (1H, dd, J = 14.3, 4.1 Hz), 1.86-1.79 (1H, m), 1.48-1.42 (1H, dd, J = 14.4, 10.1 Hz), 1.03 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 136.1, 134.5, 133.9, 129.2, 127.6, 127.5, 103.7, 77.8, 70.0, 40.6, 27.7, 18.1, 17.7. Anal. Calcd. for $C_{22}H_{28}OSi$: C, 78.51; H, 8.39. Found C, 78.34; H, 8.20.

134. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.60 (4H, m), 7.41-7.32 (6H, m), 4.52 (1H, br s), 4.33 (1H, br s), 3.92-3.88 (1H, dd, J = 11.0, 4.6 Hz), 3.26-3.21 (1H, m), 3.16-3.09 (1H, dt, J = 11.5, 2.6 Hz), 2.22-2.14 (1H, dt, J = 12.7, 5.6 Hz), 1.97 (1H, br d, J = 13.4 Hz), 1.82-1.80 (2H, m), 1.67-1.62 (1H, dd, J = 14.8, 5.5 Hz), 1.42-1.36 (1H, dd, J = 14.8, 7.7 Hz), 1.04 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 136.11,

136.07, 135.0, 134.5, 129.1, 129.0, 127.5, 108.0, 76.7, 68.3, 43.8, 34.8, 27.8, 19.0, 18.1. Anal. Calcd. for $C_{23}H_{30}OSi$: C, 78.80; H, 8.63. Found C, 78.65; H, 8.50.

135. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.59 (4H, m), 7.39-7.32 (6H, m), 4.60 (1H, br s), 4.38 (1H, br d, J = 2.4 Hz), 3.68-3.62 (1H, td, J = 12.4, 4.4 Hz), 3.47-3.40 (1H, m), 2.97-2.90 (1H, m), 2.27- 2.07 (4H, m), 1.70-1.58 (1H, m), 1.65-1.60 (1H, dd, J = 15.0, 6.7 Hz), 1.57-1.45 (1H, m), 1.42-1.36 (1H, dd, J = 15.0, 6.4Hz), 1.03 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 136.1, 129.0, 128.9, 127.5, 127.4, 112.0, 77.9, 69.7, 47.5, 34.4, 30.0, 27.8, 18.1. Anal. Calcd. for $C_{24}H_{32}OSi$: C, 79.06; H, 8.85. Found C, 78.85; H, 8.70.

136. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.57 (4H, m), 7.38-7.32 (6H, m), 5.55-5.48 (1H, td, J = 15.4, 7.8 Hz), 5.27 (1H, d, J = 15.4 Hz), 3.76-3.69 (1H, m), 3.59-3.54 (1H, m), 2.12-2.10 (2H, dd, J = 7.8, 1.2 Hz), 1.76-1.68 (1H, m), 1.63-1.53 (2H, m), 1.57 (3H, s), 1.51-1.45 (1H, m), 1.06 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 135.5, 134.5, 129.0, 127.5, 123.2, 82.1, 67.1, 37.3, 27.9, 26.6, 25.4, 18.4, 16.6. Anal. Calcd. for $C_{24}H_{32}OSi$: C, 79.06; H, 8.85. Found C, 78.90; H, 8.74.

137a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.60 (4H, m), 7.44-7.35 (6H, m), 6.01-5.95 (1H, m), 4.54-4.48 (1H, m), 2.31- 2.23 (1H, m), 2.13-2.05 (1H, m), 2.07 (3H, d, J = 7.3 Hz), 2.02-1.97 (1H, dd, J = 14.4, 3.6 Hz), 1.53-1.47 (1H, dd, J = 14.4, 10.7 Hz), 1.05 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 137.8, 136.0, 133.9, 132.9, 129.59, 129.56, 127.9, 127.8, 126.1, 76.6, 37.5, 27.6, 19.0, 18.1, 13.9. Anal. Calcd. for $C_{23}H_{28}O_2Si$: C, 75.78; H, 7.74. Found C, 75.60; H, 7.60.

137b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.60 (4H, m), 7.45-7.34 (6H, m), 6.64-6.58 (1H, m), 4.62-4.55 (1H, m), 2.28-2.21 (1H, tdd, J = 17.0, 7.7, 2.0 Hz), 2.02-1.98 (1H, dd, J = 14.2, 3.9 Hz), 2.02-1.94 (1H, m) 1.57-1.54 (3H, td, J = 7.1, 1.7 Hz), 1.51-1.44 (1H, dd, J = 14.4, 10.8 Hz), 1.04 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 136.0, 134.9, 133.9, 132.8, 129.6, 127.9, 76.8, 33.0, 27.6, 19.5, 18.0, 15.4. Anal. Calcd. for $C_{23}H_{28}O_2Si$: C, 75.78; H, 7.74. Found C, 75.62; H, 7.60.

138. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.62 (4H, m), 7.44-7.36 (6H, m), 5.64 (1H, m), 4.43-4.36 (1H, tt, J = 11.0, 3.5 Hz), 2.01-1.96 (1H, dd, J = 14.7, 3.7 Hz), 1.94-1.85 (3H, m), 1.65-1.59 (1H, dd, J = 14.7, 10.6 Hz), 1.60-1.55 (1H, dd, J = 17.8, 3.7 Hz), 1.04 (9H, s), 0.83 (3H, t, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 162.3, 136.0, 134.1, 132.8, 129.61, 129.58, 128.0, 127.9, 114.2, 76.3, 35.1, 29.3, 27.6, 18.1, 17.8, 10.5. ν_{max} (film) 3050, 2930, 1710, 1261 cm^{-1}. Anal. Calcd. for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99. Found C, 75.90; H, 7.80.

139a (major isomer). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.57 (4H, m), 7.41-7.34 (6H, m), 4.42 (1H, q, J = 6.4 Hz), 2.50 (1H, d, J = 18.3 Hz), 2.13 (1H, d, J = 18.3 Hz), 1.37-1.33 (1H, dd, J = 14.4, 4.1 Hz), 1.26 (3H, d, J = 6.3 Hz), 1.06 (9H, s), 0.93-0.85 (1H, m), 0.82-0.76 (1H, dd, J = 14.6, 8.8 Hz), 0.67-0.63 (1H, dd, J = 8.7, 5.7 Hz), 0.15 (1H, t, J = 5.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 136.0, 135.8, 134.2, 134.1, 129.4, 129.3, 127.8, 127.7, 77.2, 37.9, 27.8, 26.7, 20.2, 20.1, 18.1, 17.1, 10.5. Anal. Calcd. for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99. Found C, 76.00; H, 7.84.

139b (1:1 mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.58 (8H, m), 7.42-7.35 (12H, m), 4.24 (1H, q, *J* = 6.4 Hz), 4.09 (1H, q, *J* = 6.4 Hz), 2.72 (1H, d, *J* = 18.1 Hz), 2.45 (1H, d, *J* = 18.1 Hz), 2.38 (1H, d, *J* = 18.0 Hz), 2.25 (1H, d, *J* = 18.1 Hz), 1.46-1.41 (1H, dd, *J* = 18.9, 3.4 Hz), 1.25-1.20 (1H, dd, *J* = 14.9, 5.4 Hz), 1.06 (9H, s), 1.05 (9H, s), 1.08-1.02 (1H, m), 0.99 (3H, d, *J* = 6.3 Hz), 0.98-0.88 (1H, m), 0.94 (3H, d, *J* = 6.4 Hz), 0.83-0.79 (1H, dd, *J* = 9.2, 5.2 Hz), 0.80-0.69 (1H, m), 0.77-0.71 (1H, dd, *J* = 14.9, 9.3 Hz), 0.62-0.58 (1H, dd, *J* = 9.2, 5.2 Hz), 0.18 (1H, t, *J* = 5.6 Hz), 0.02 (1H, t, *J* = 5.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 175.8, 136.01, 135.97, 135.9, 135.8, 134.3, 134.2, 134.11, 134.07, 129.4, 129.30, 129.28, 127.80, 127.75, 127.7, 82.0, 80.8, 33.5, 33.0, 28.0, 27.8, 27.7, 20.0, 18.14, 18.09, 17.2, 17.1, 17.0, 15.8, 14.3, 11.42, 11.41. Anal. Calcd. for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99. Found C, 75.95; H, 7.80.

Typical procedure for the conversion of 139b into 140a and 140b

To a solution of **139b** (0.017 g, 0.045 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was added a solution of BF_3•OEt_2 (0.008 g, 0.054 mmol) in anhydrous CH_2Cl_2 (0.4 mL) at 0 °C. The resulting mixture was warmed gradually to rt. After stirring for 10 h, Et_2O (10 mL) was added to it and the etheral solution was washed with saturated aq NH_4Cl (2 x 5 mL). The combined aq washings were extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with water and brine and dried. Removal of solvents furnished the crude product, which was purified by column chromatography

(EtOAc/hexanes) to isolate a 13:1 mixture of **140a** and **140b**, 0.015 g, 89%, colorless viscous liquid.

140a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.64 (4H, m), 7.45-7.36 (6H, m), 5.19 (1H, br d, J = 6.8 Hz), 4.42-4.36 (1H, tt, J = 10.6, 3.5 Hz), 3.13-2.89 (2H, m), 2.06 (1H, br d, J = 16.8 Hz), 2.01-1.97 (1H, dd, J = 14.6, 3.9 Hz), 1.88-1.78 (1H, m), 1.60-1.54 (1H, dd, J = 14.6, 10.0 Hz), 1.18 (3H, d, J = 6.4 Hz), 1.05 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 136.0, 134.0, 132.9, 129.6, 129.56, 128.0, 127.8, 126.5, 121.1, 76.9, 38.8, 34.0, 27.6, 18.2, 18.1, 12.9. ν_{max} (film) 3056, 2932, 1746, 1253 cm^{-1}. Anal. Calcd. for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99. Found C, 76.02; H, 7.88.

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36. Except for the reactions involving allyltrimethylsilane, **49d**, the amount of the recovered allylsilane from the reactions of **49a-49c** was more than 90% in all the cases.

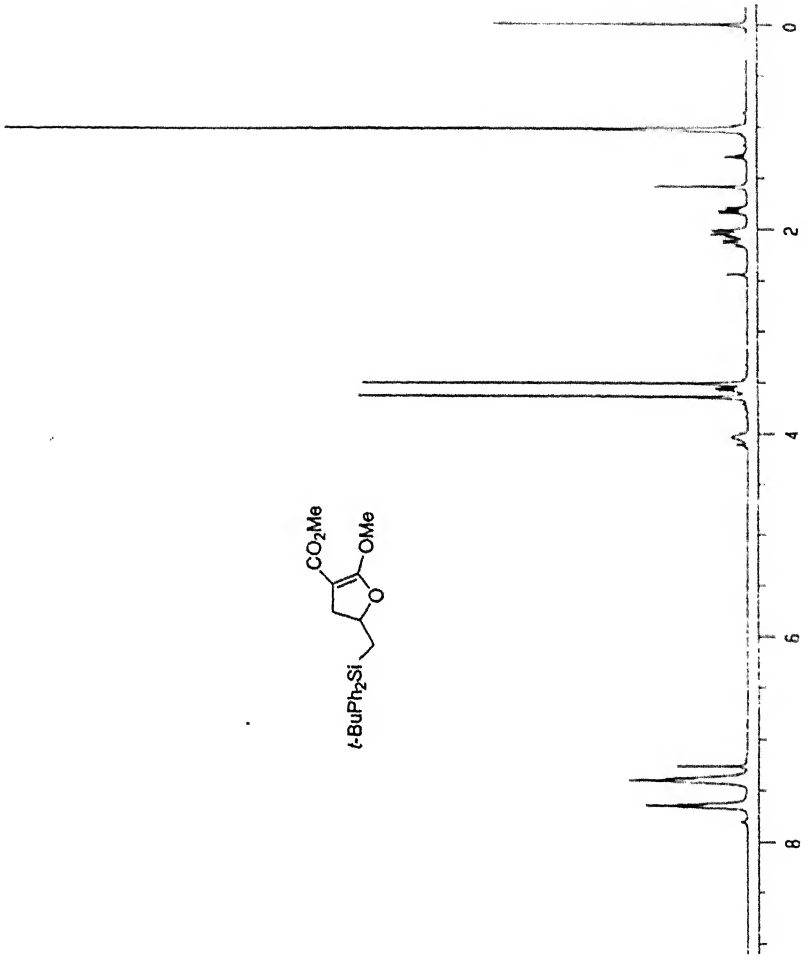


Figure 8. 400 MHz ^{1}H NMR spectrum of **81**

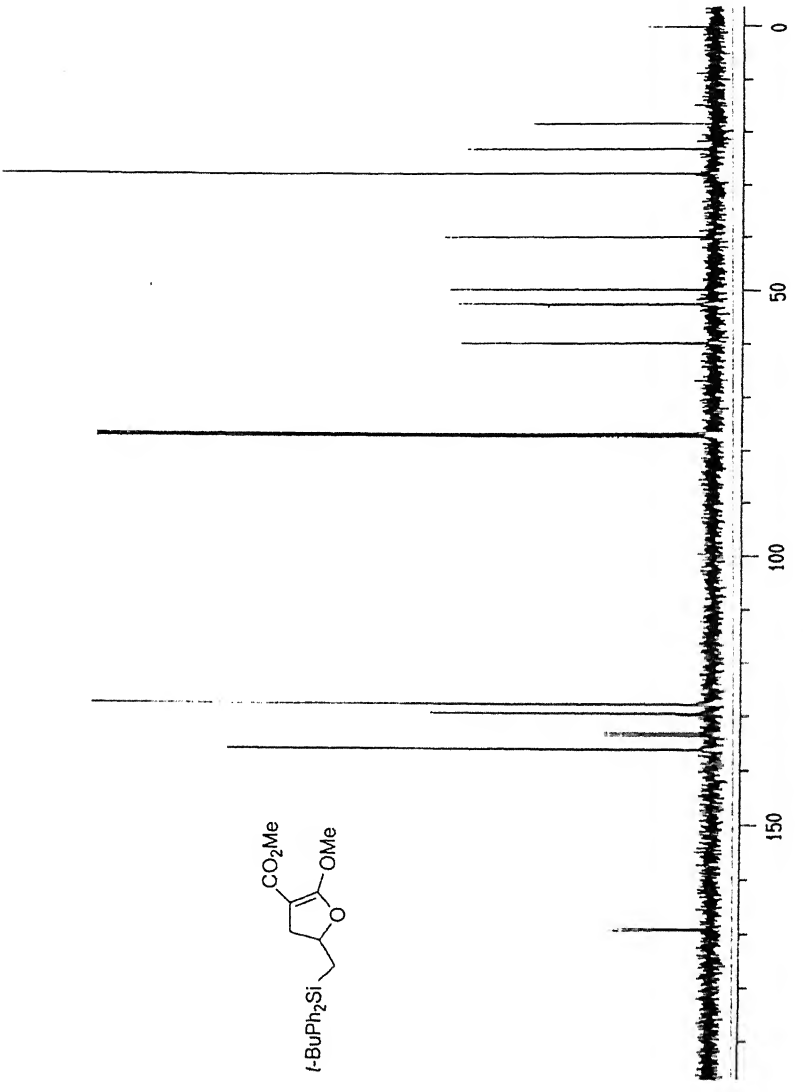


Figure 9. 100 MHz ^{13}C NMR spectrum of **81**

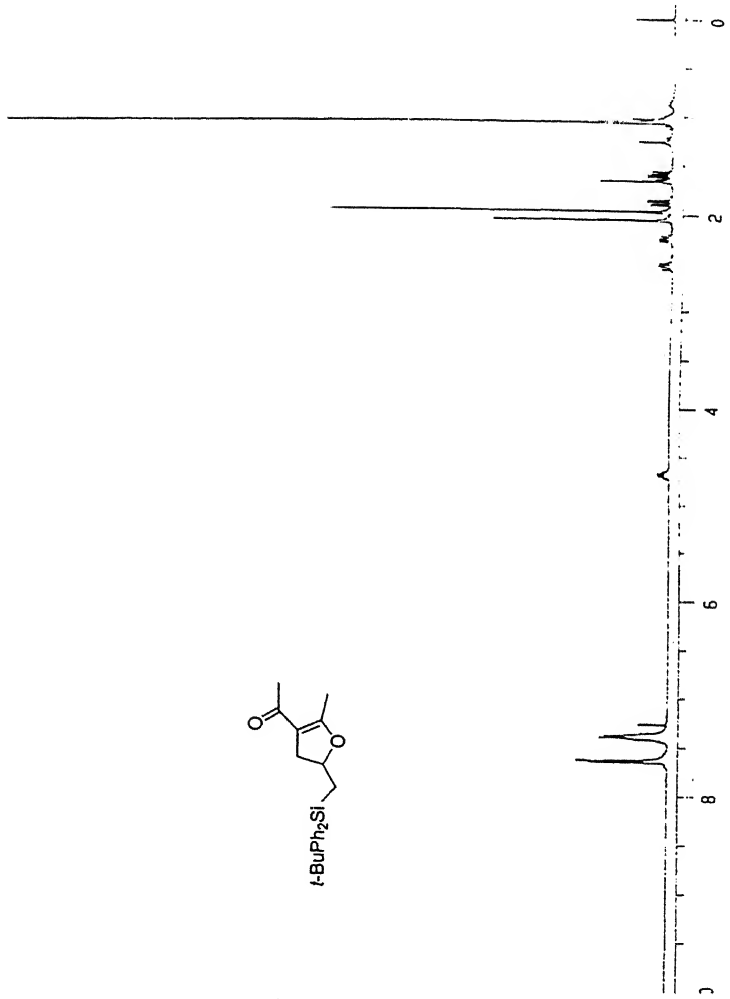


Figure 10. 400 MHz ^{1}H NMR spectrum of **82**

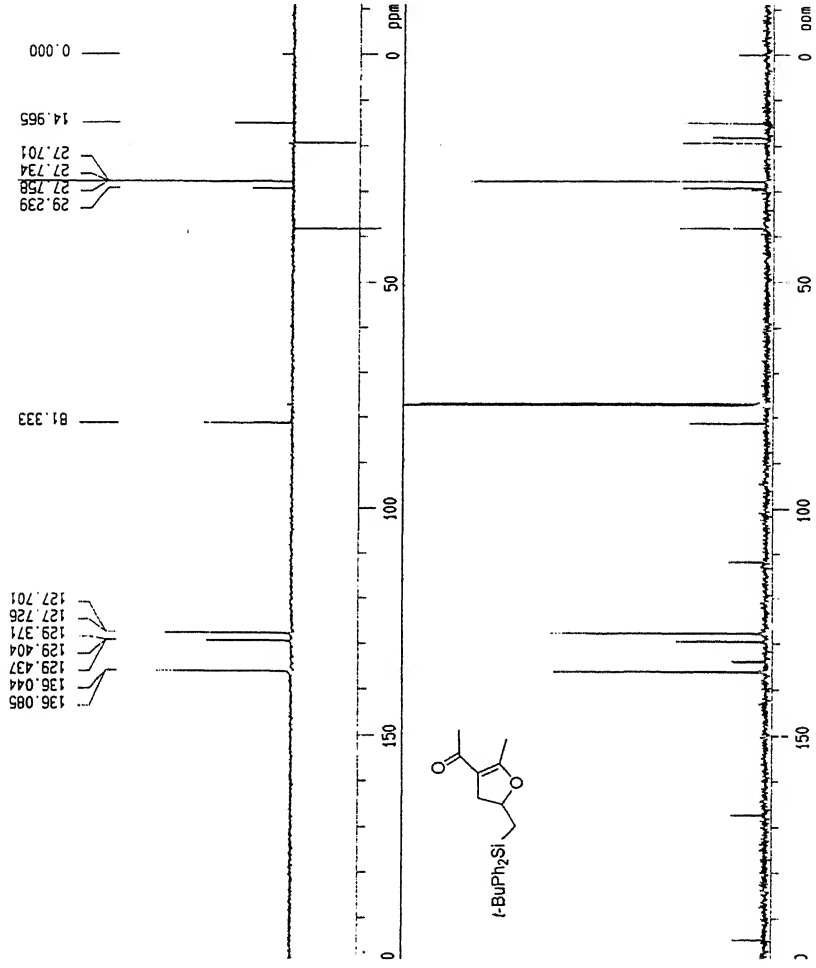


Figure 11. 100 MHz ^{13}C NMR and DEPT spectra of **82**

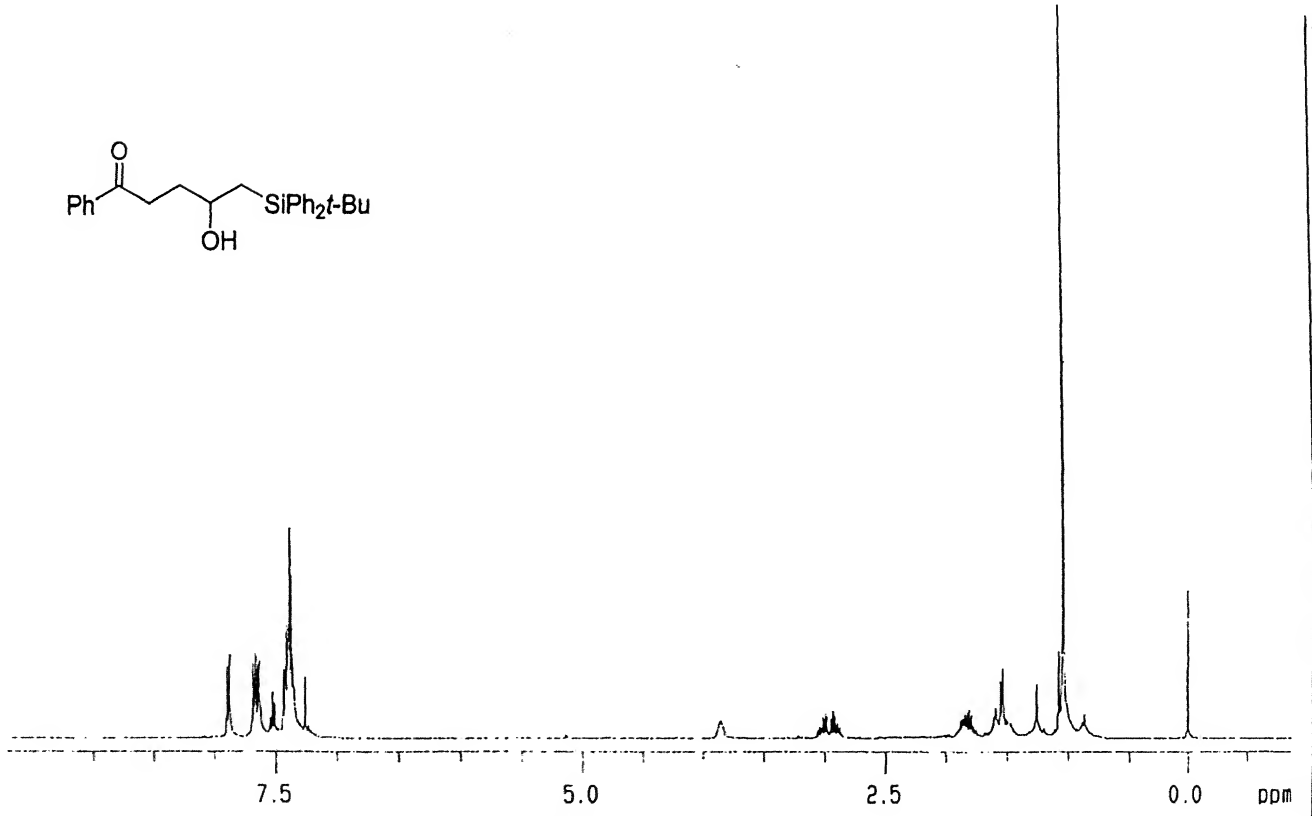


Figure 12. 400 MHz ^{1}H NMR spectrum of **85**

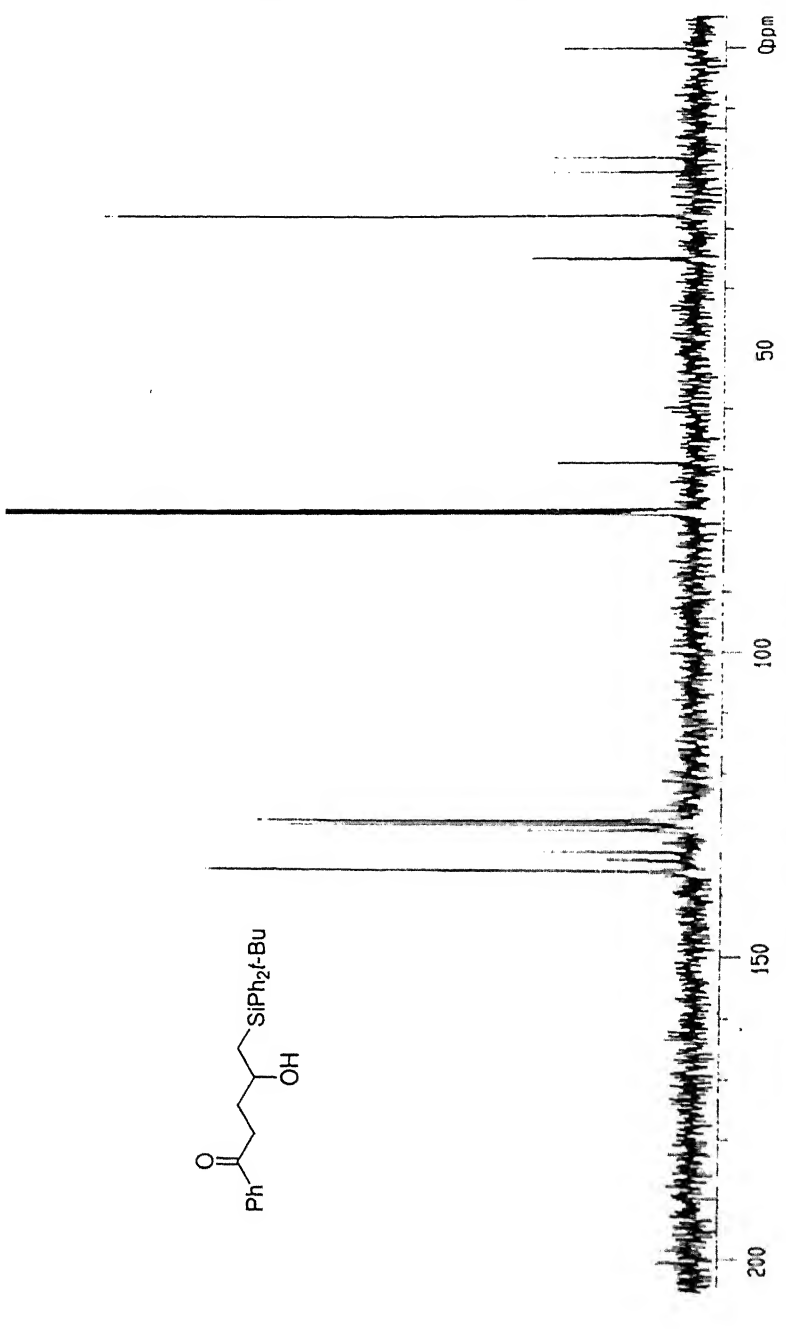


Figure 13. 100 MHz ^{13}C NMR spectrum of **85**

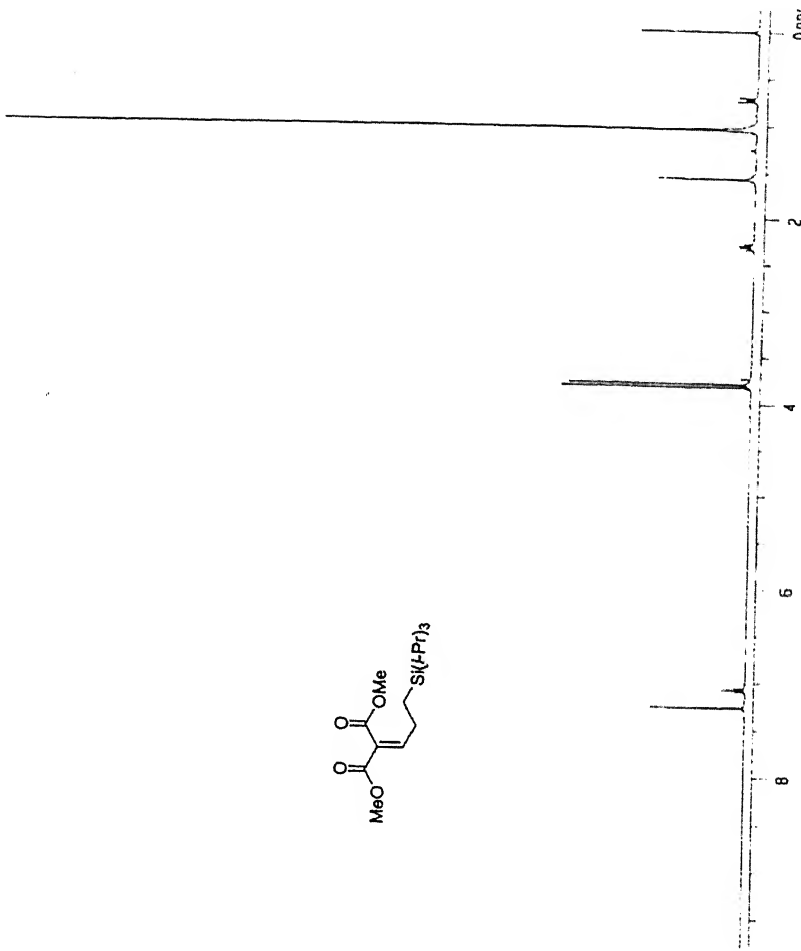


Figure 14. 400 MHz ^{1}H NMR spectrum of **86**

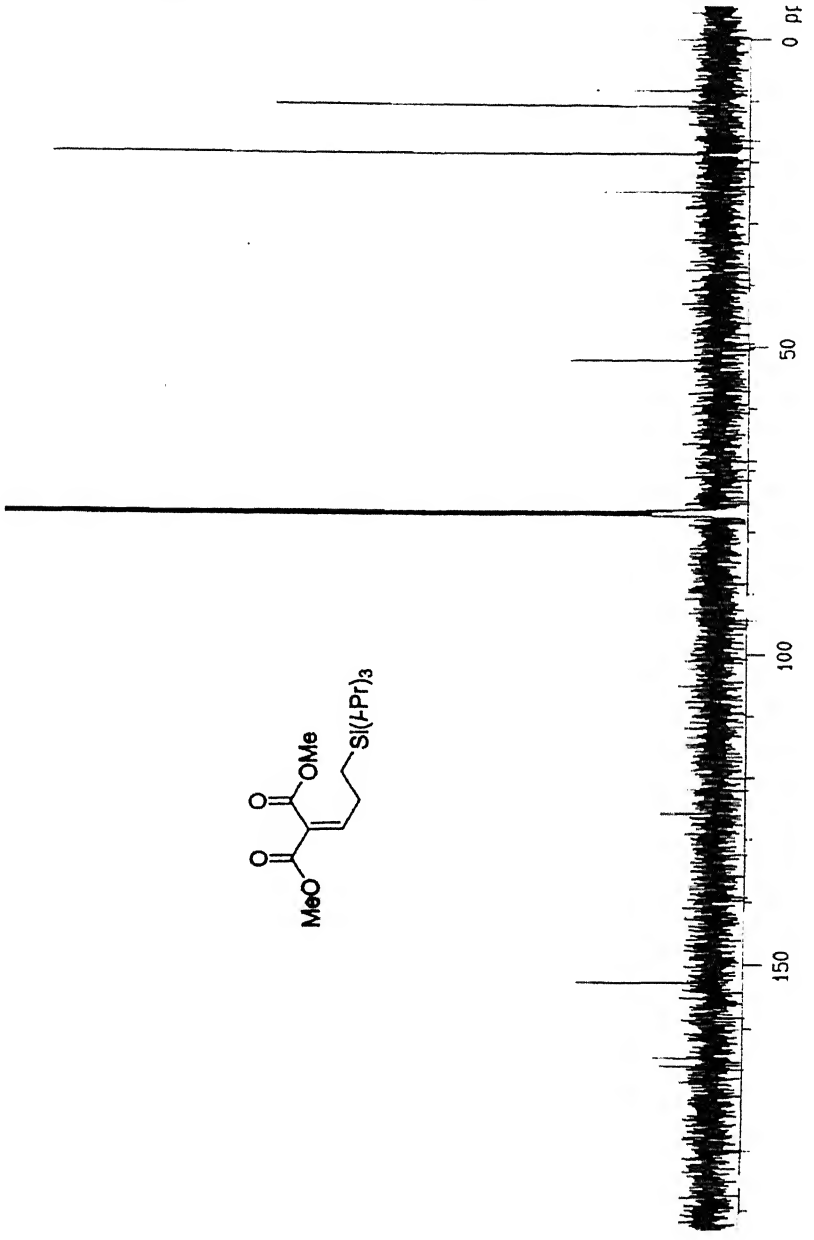


Figure 15. 100 MHz ^{13}C NMR spectrum of **86**

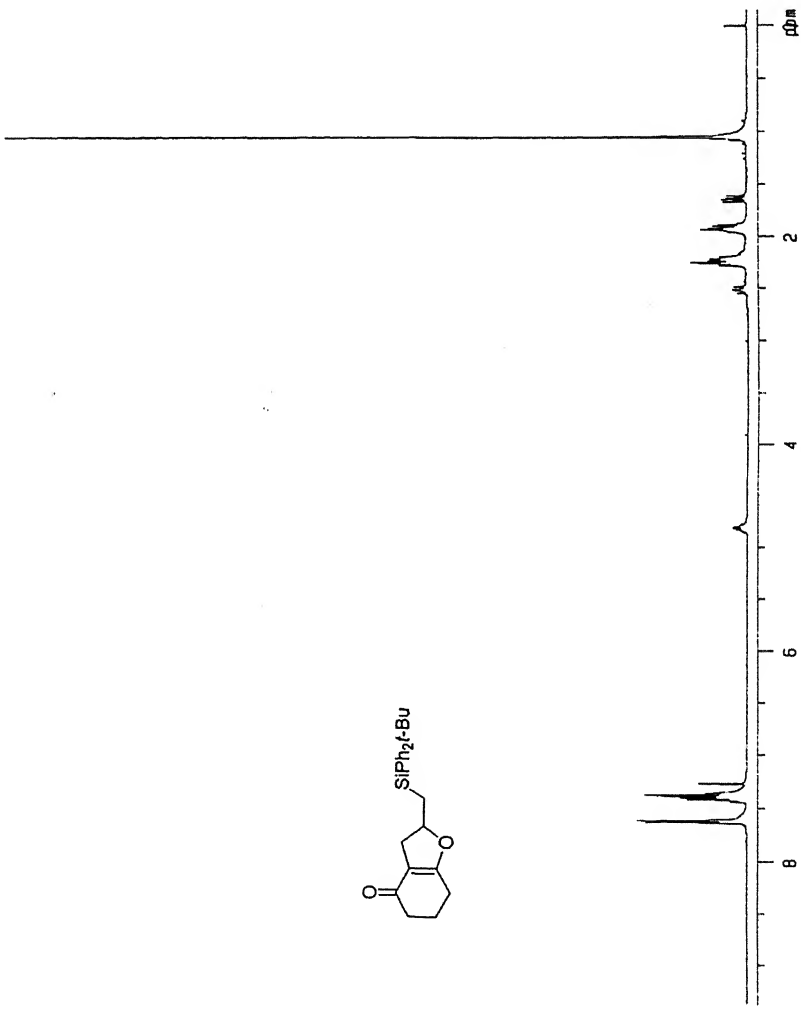


Figure 16. 400 MHz ^{1}H NMR spectrum of **92**

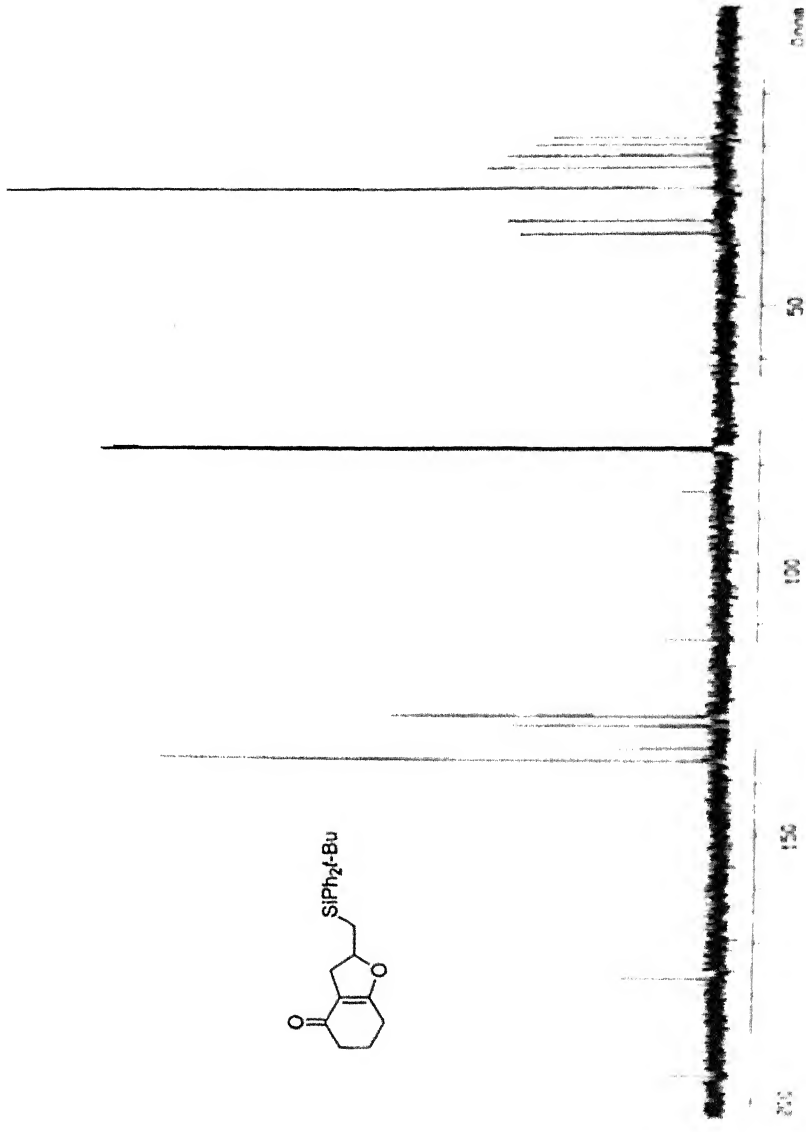


Figure 17 100 MHz ^{13}C NMR spectrum of **92**

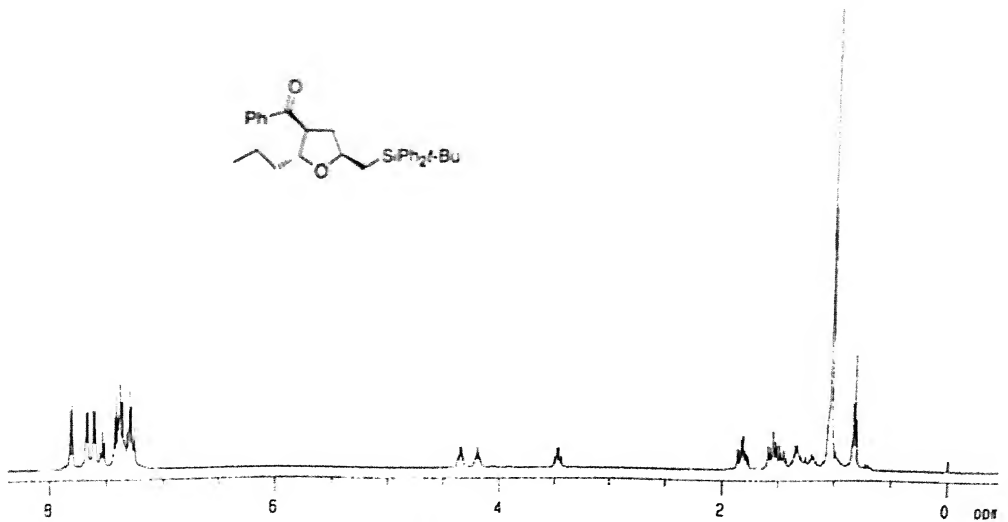


Figure 18. 400 MHz ^{1}H NMR spectrum of **100**

Figure 19 (a) 300 MHz ^{1}C NMR spectrum of **100**

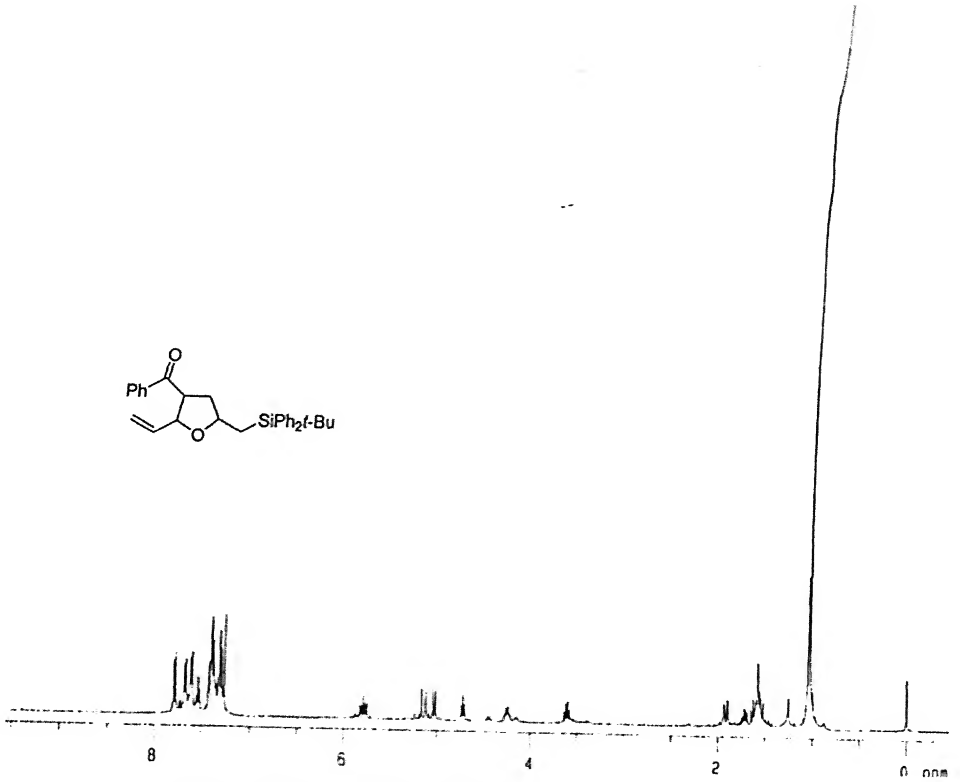


Figure 20. 400 MHz ^{1}H NMR spectrum of **101**

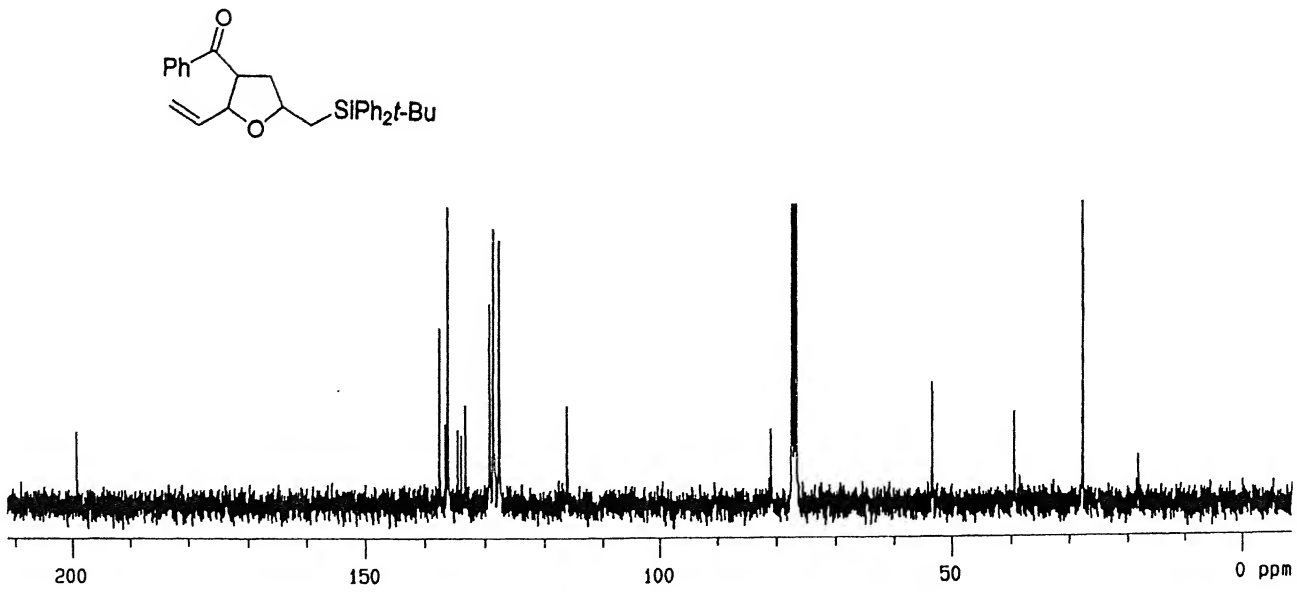


Figure 21. 100 MHz ^{13}C NMR spectrum of **101**

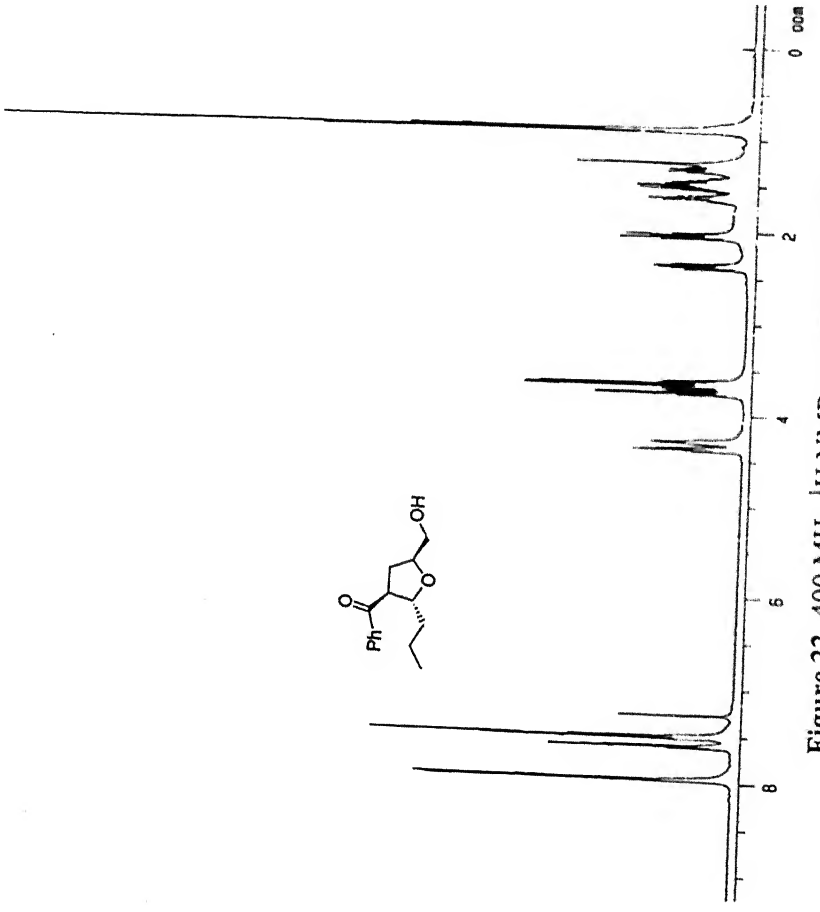


Figure 22. 400 MHz ^{1}H NMR spectrum of **106a**

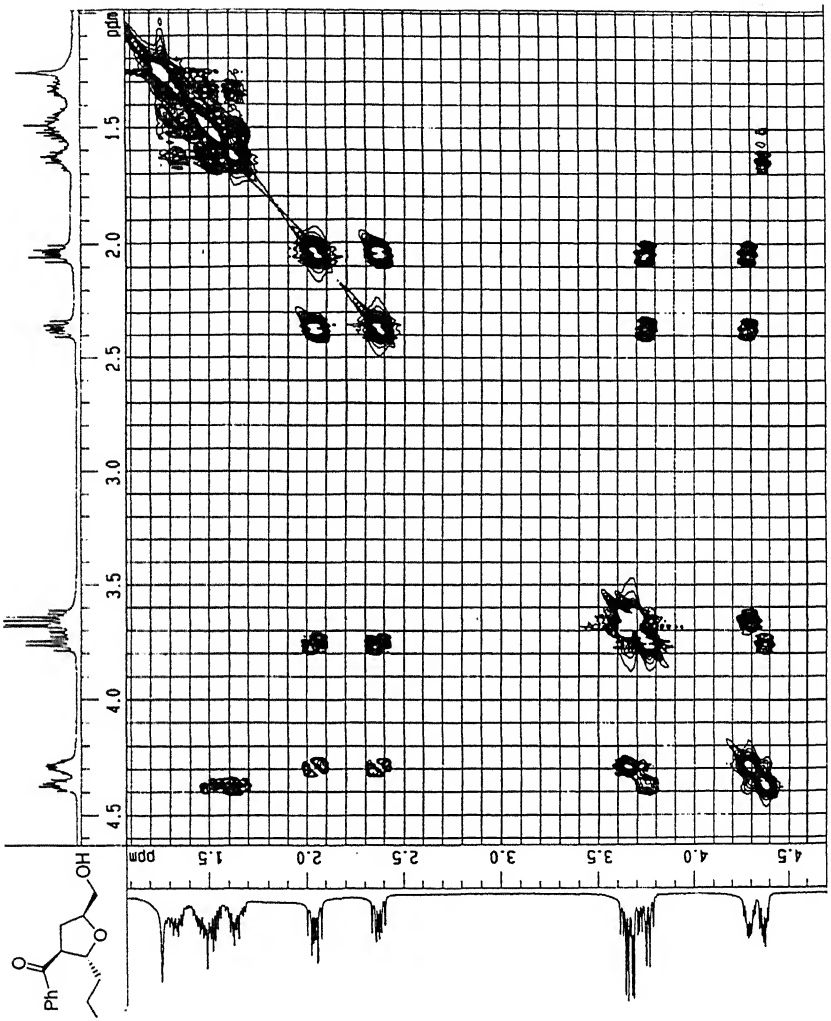


Figure 23. 400 MHz COSY spectrum of **106a**

Figure 24. 100 MHz ^{13}C NMR spectrum of 106a

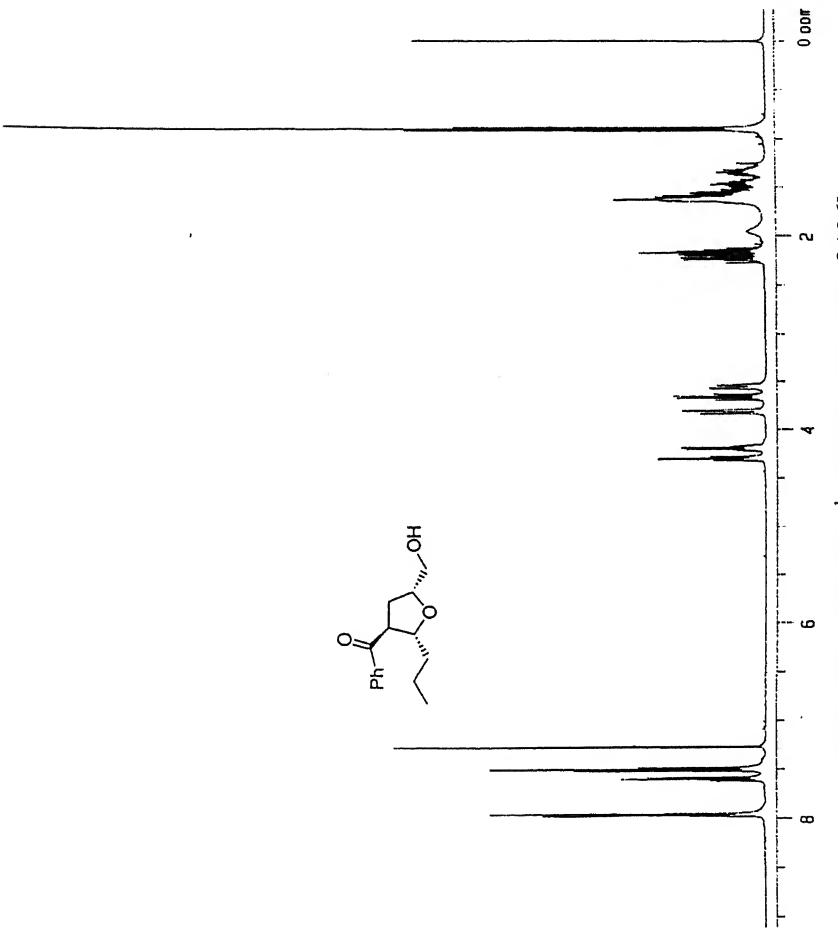


Figure 25. 400 MHz ^{1}H NMR spectrum of **106b**

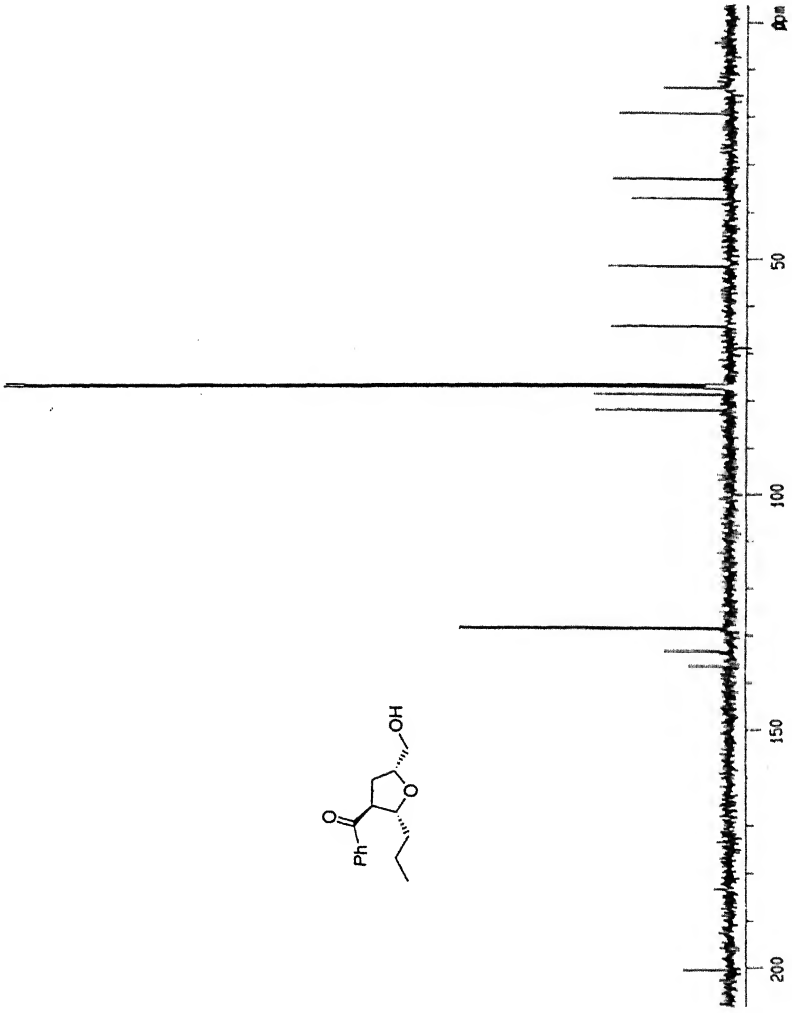


Figure 26. 100 MHz ^{13}C NMR spectrum of 106b

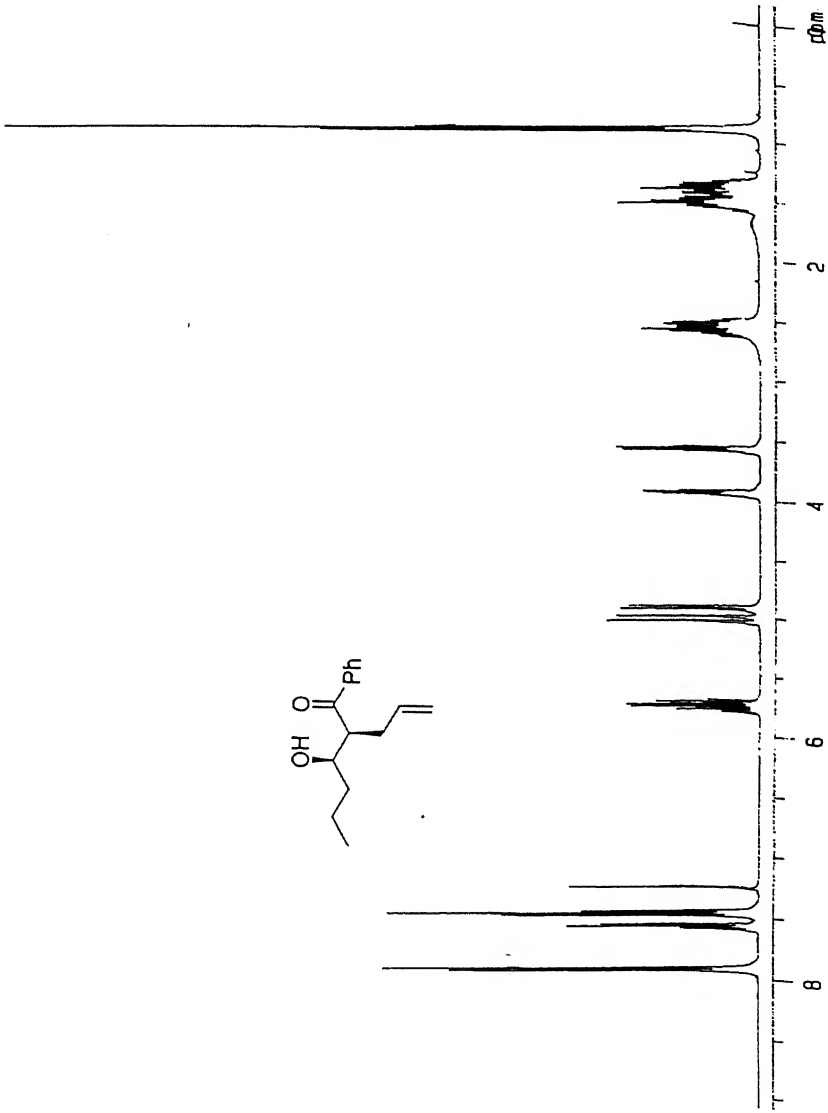


Figure 27. 400 MHz ^{1}H NMR spectrum of **107**

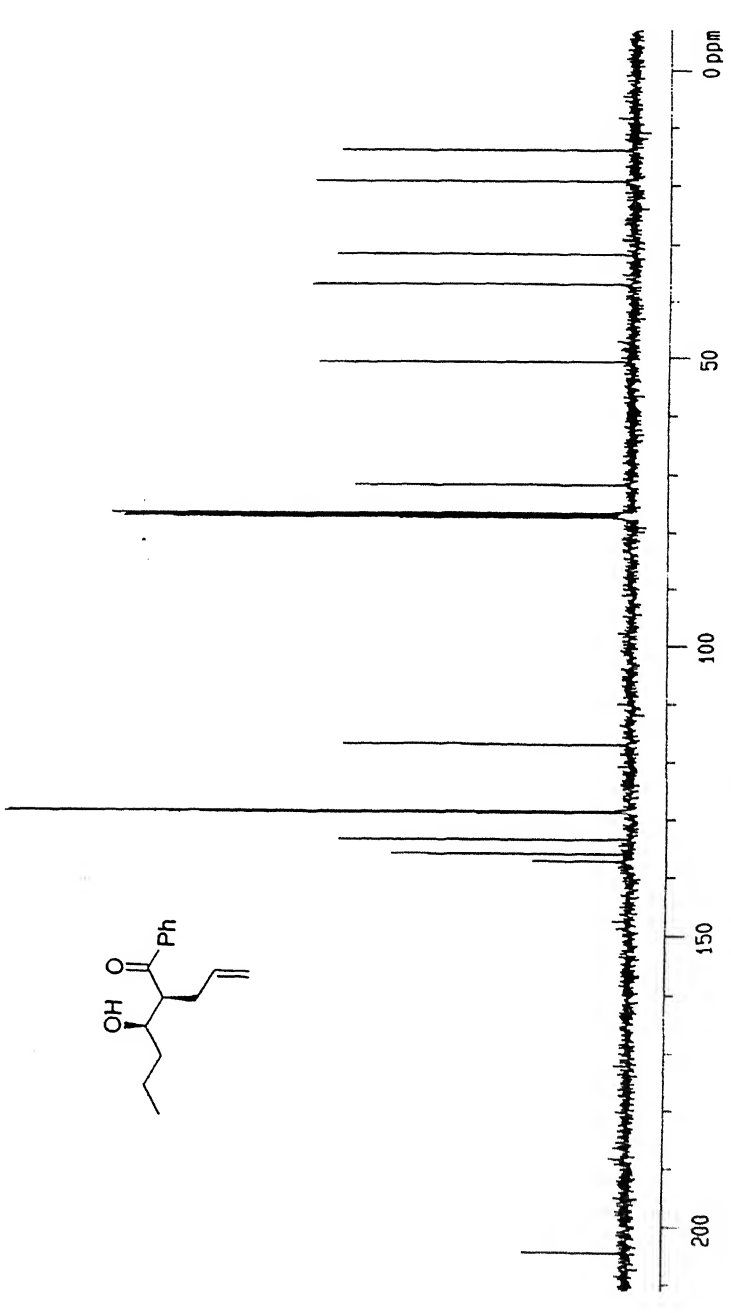


Figure 28. 100 MHz ^{13}C NMR spectrum of **107**

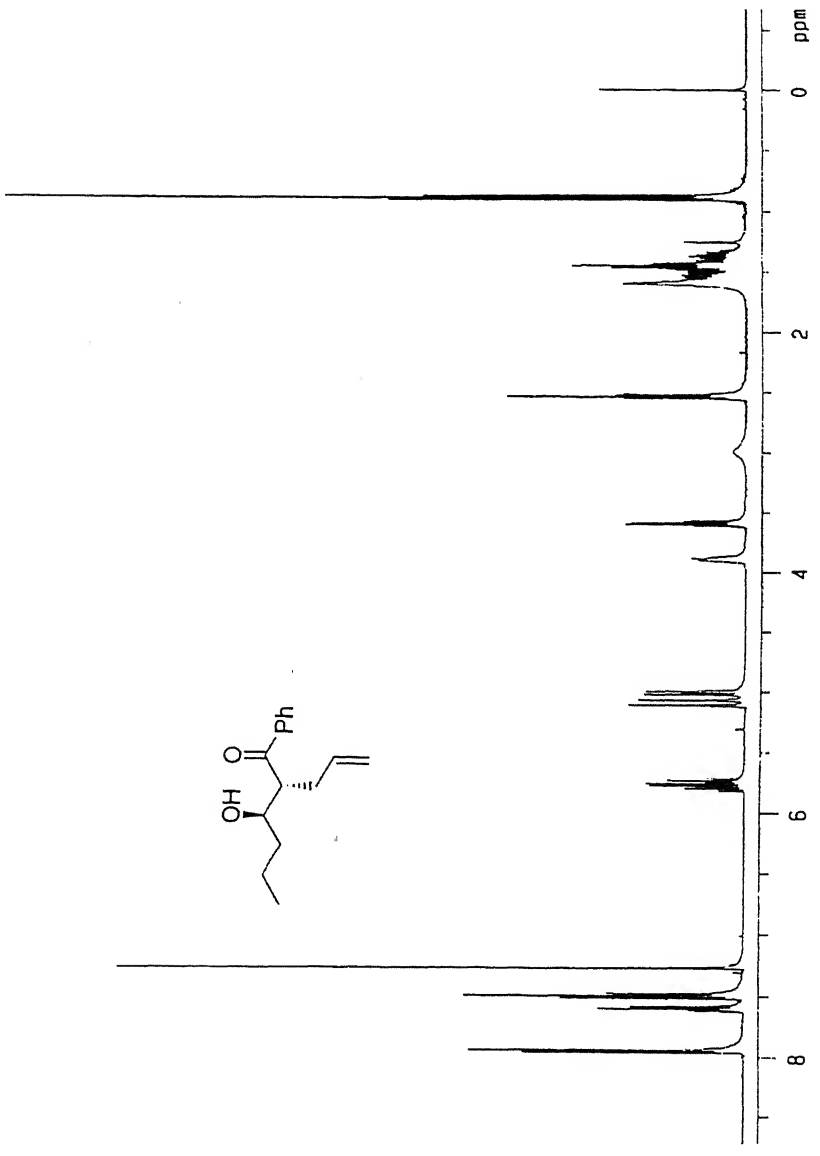


Figure 29. 400 MHz ^{1}H NMR spectrum of **108**

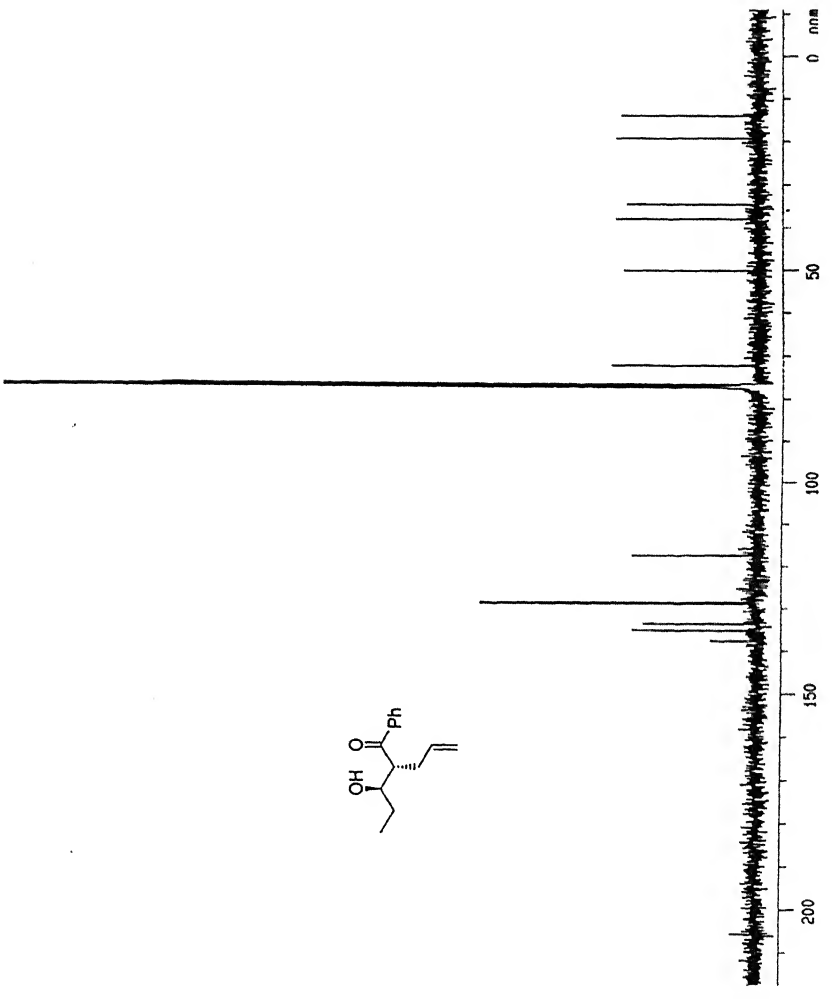


Figure 30. 100 MHz ^{13}C NMR spectrum of **108**

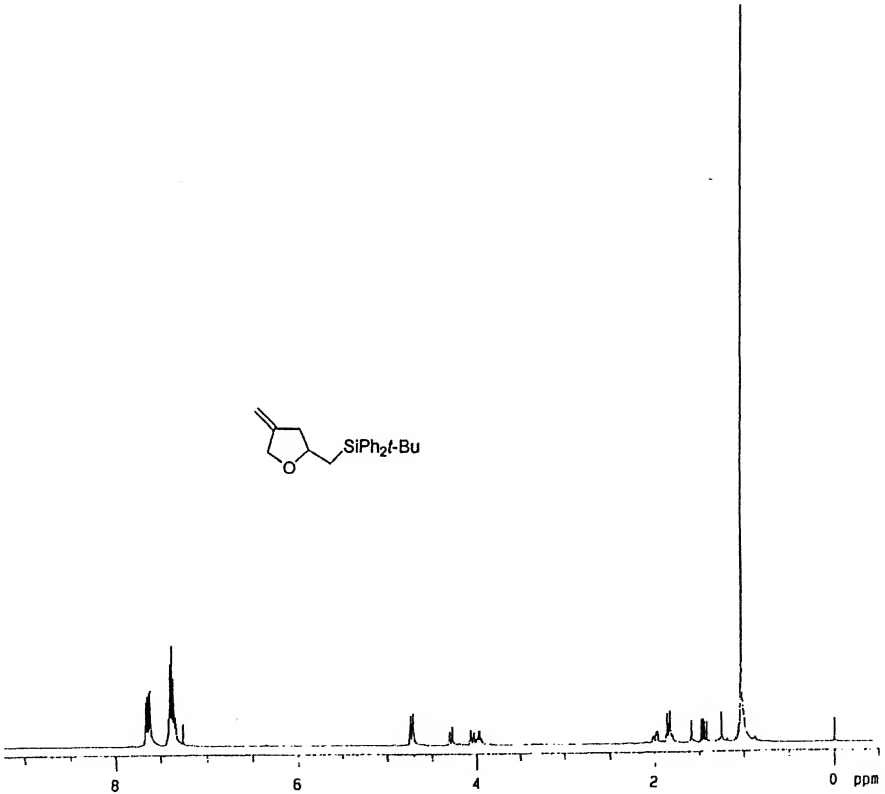


Figure 31. 400 MHz ^{1}H NMR spectrum of **133**

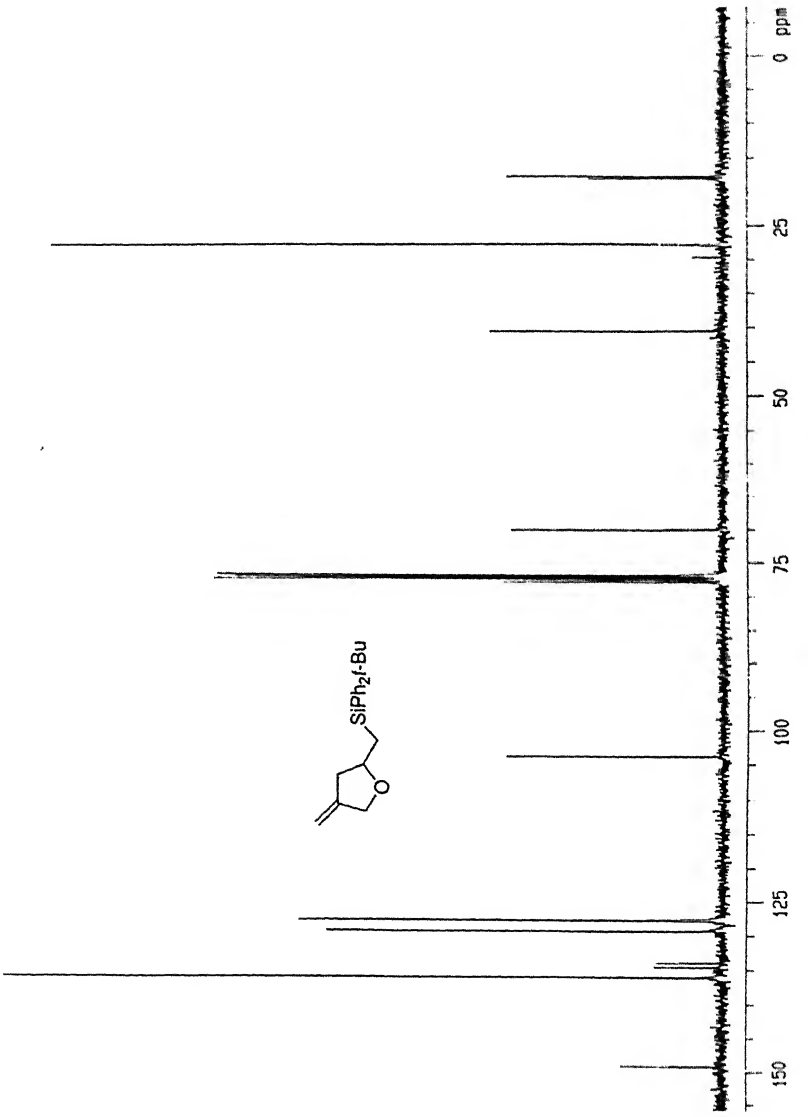


Figure 32. 100 MHz ^{13}C NMR spectrum of **133**

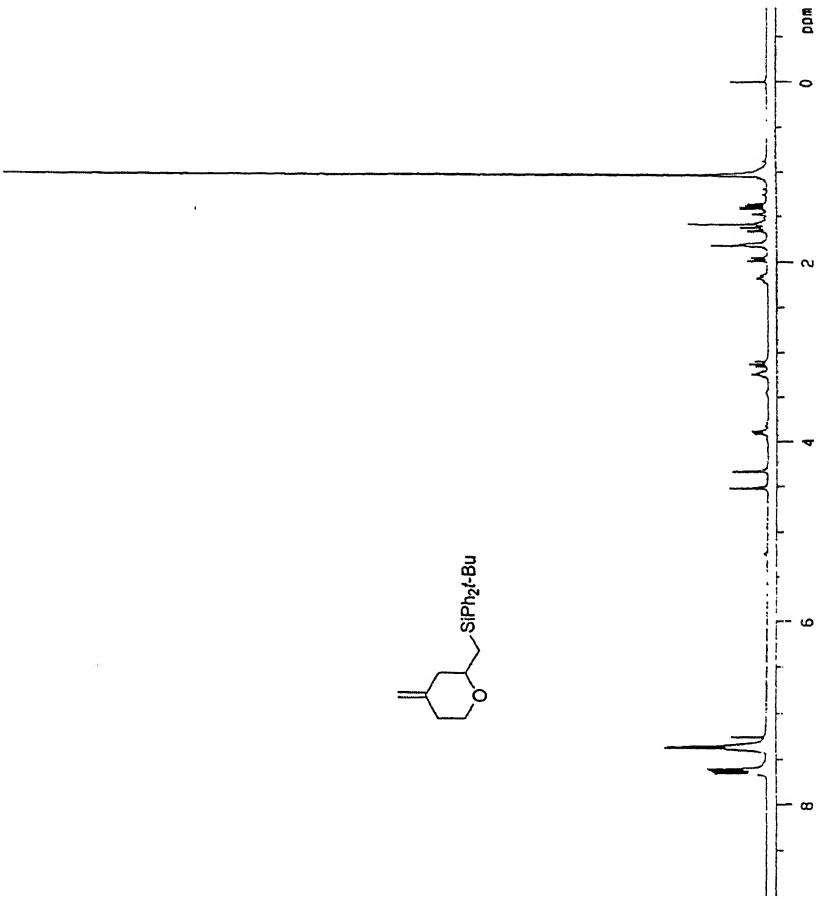


Figure 33. 400 MHz ^{1}H NMR spectrum of **134**

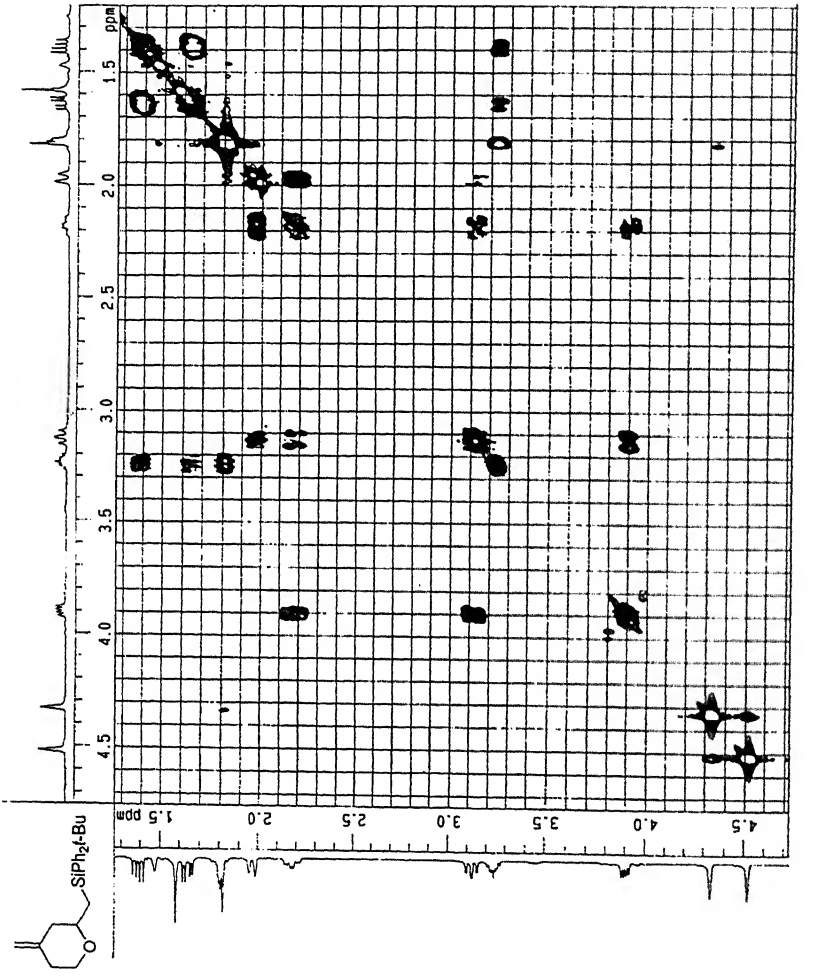


Figure 34. 400 MHz COSY spectrum of 134

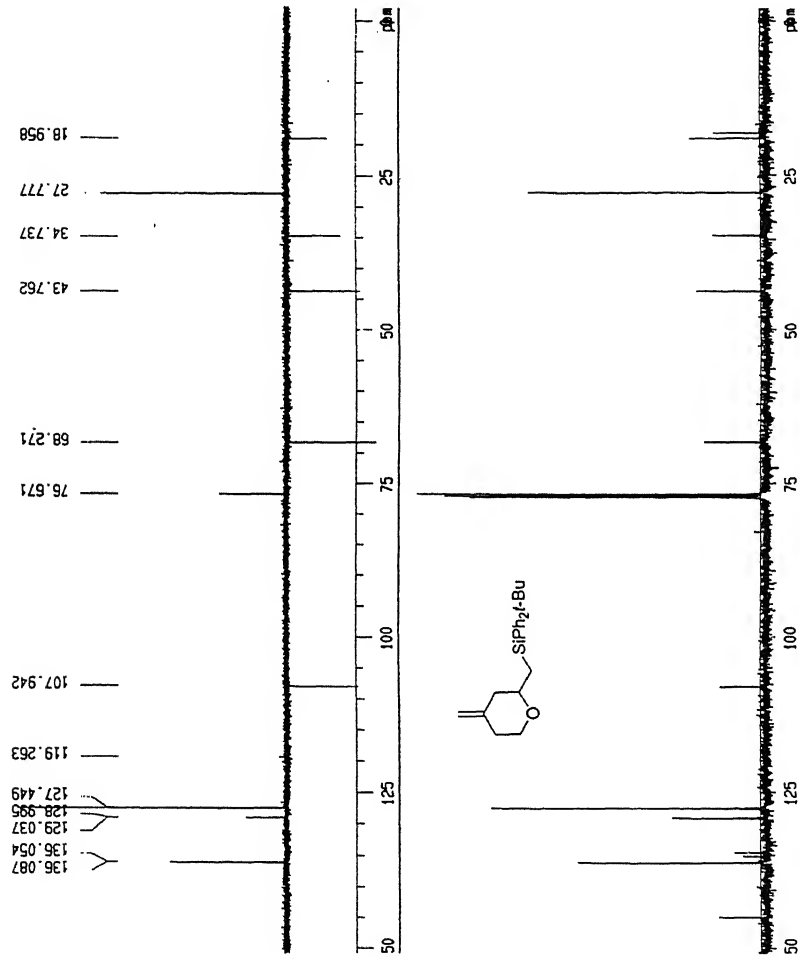


Figure 35. 100 MHz ^{13}C NMR and DEPT spectra of **134**

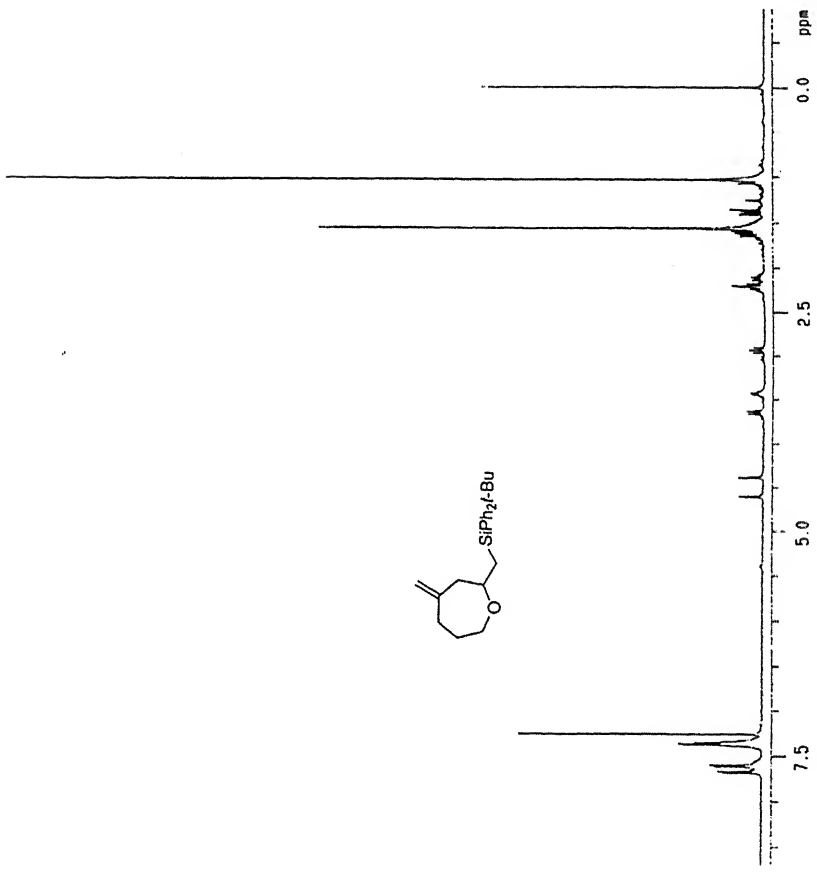


Figure 36. 400 MHz ^{1}H NMR spectrum of **135**

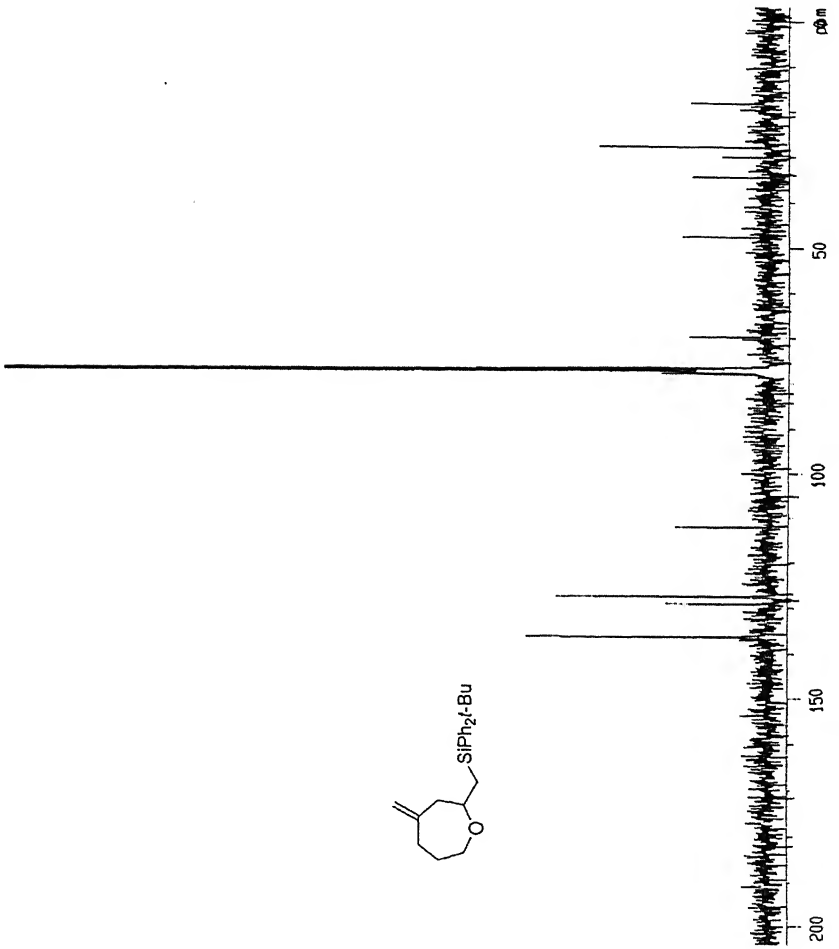


Figure 37. 100 MHz ^{13}C NMR spectrum of **135**

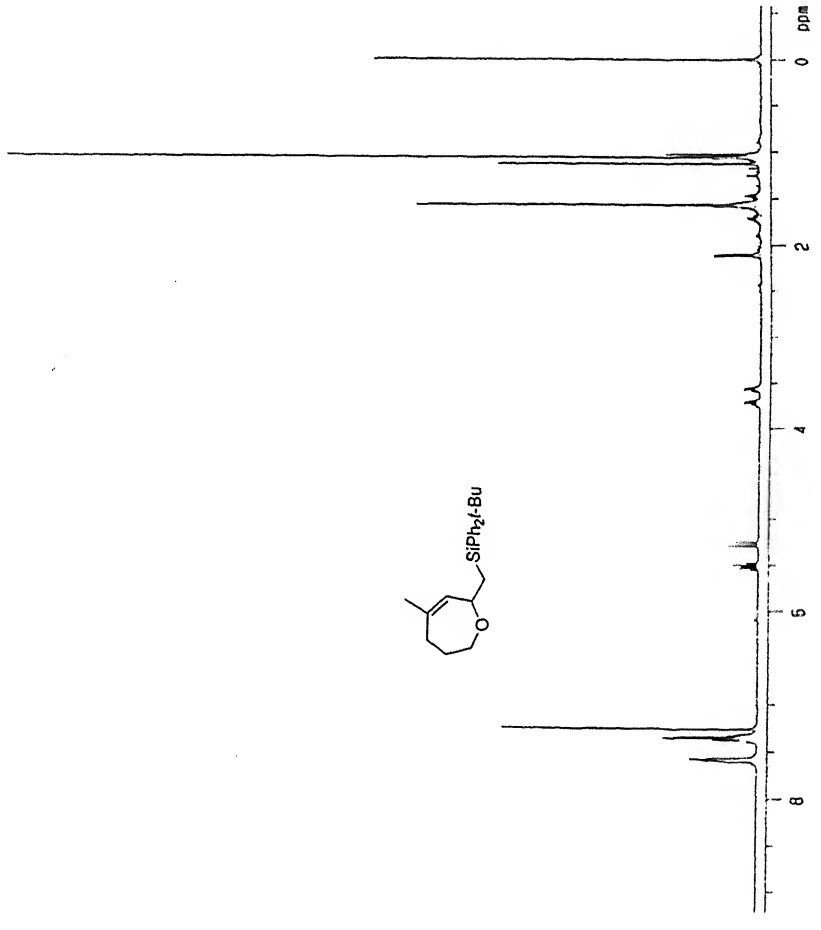


Figure 38. 400 MHz ^{1}H NMR spectrum of **136**

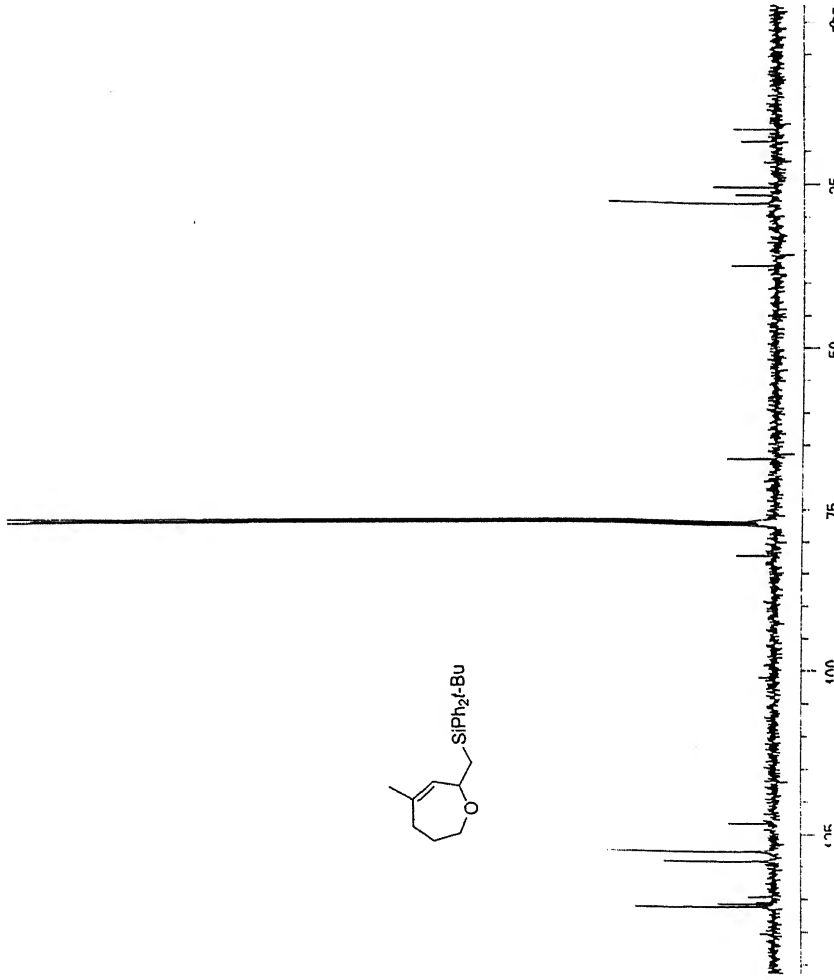


Figure 39. 100 MHz ^{13}C NMR spectrum of **136**

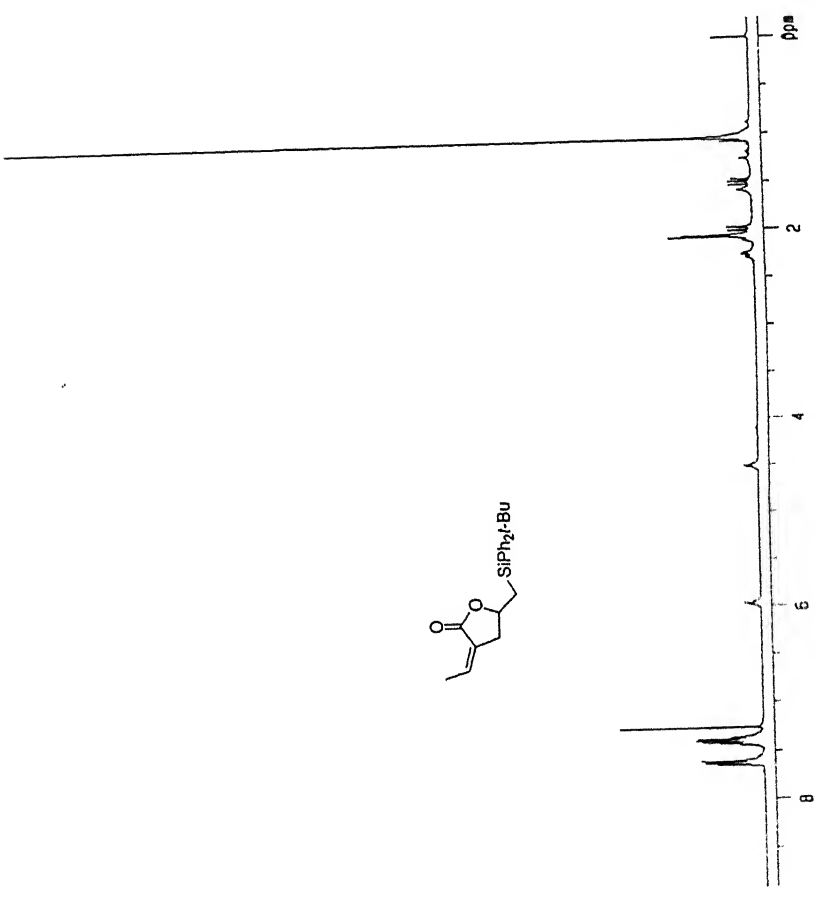


Figure 40. 400 MHz ^{1}H NMR spectrum of **137a**

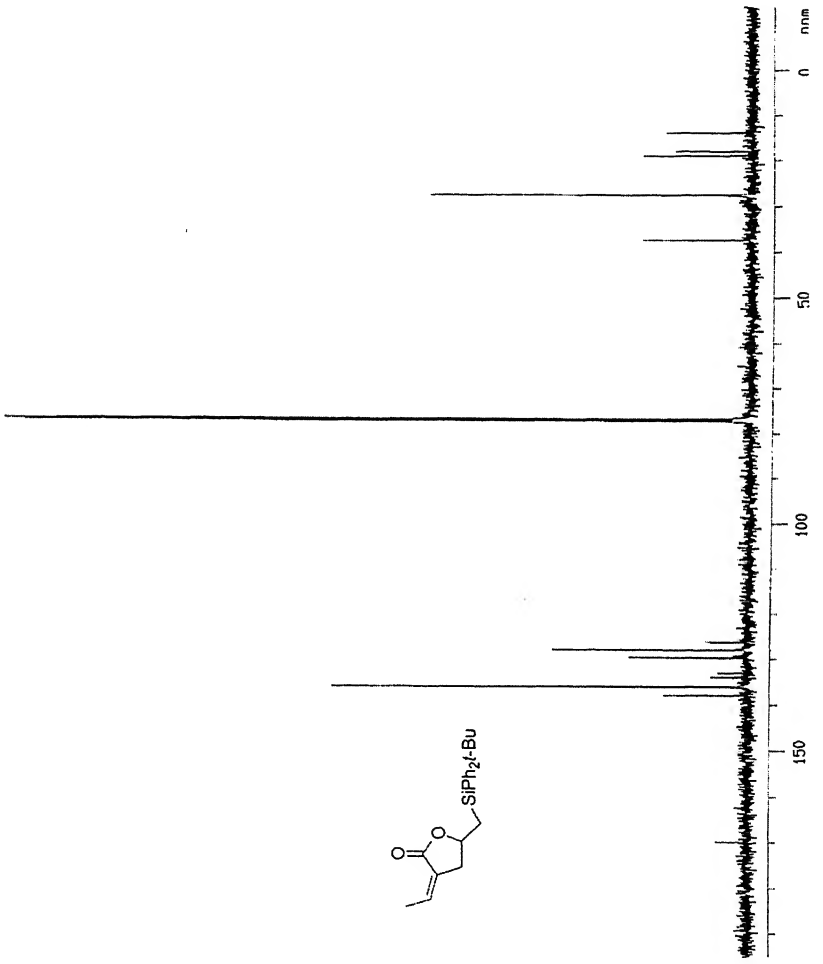


Figure 41. 100 MHz ^{1}H NMR spectrum of **137a**

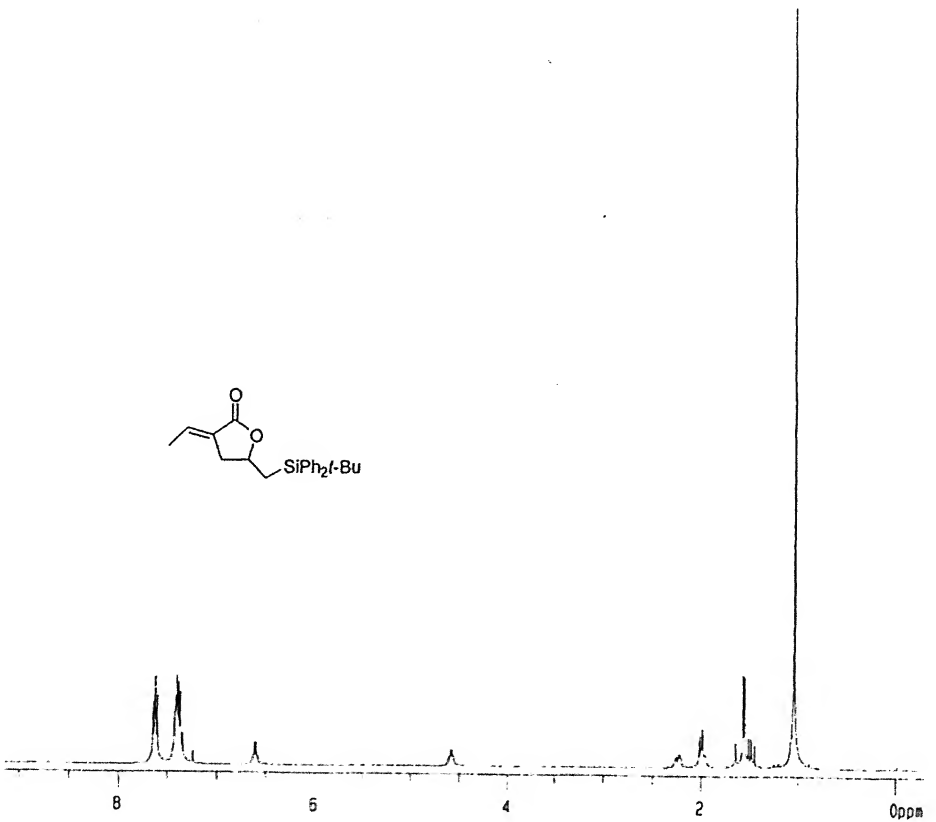


Figure 42. 400 MHz ^{1}H NMR spectrum of **137b**

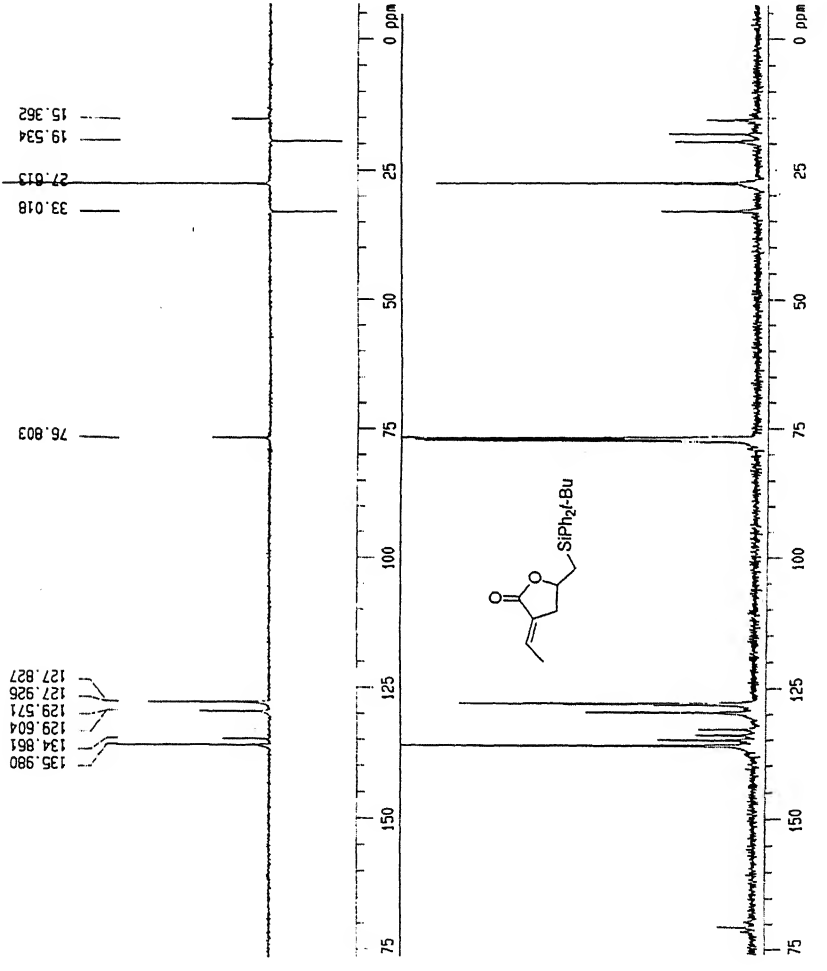


Figure 43. 100 MHz ^{13}C NMR and DEPT spectra of **137b**

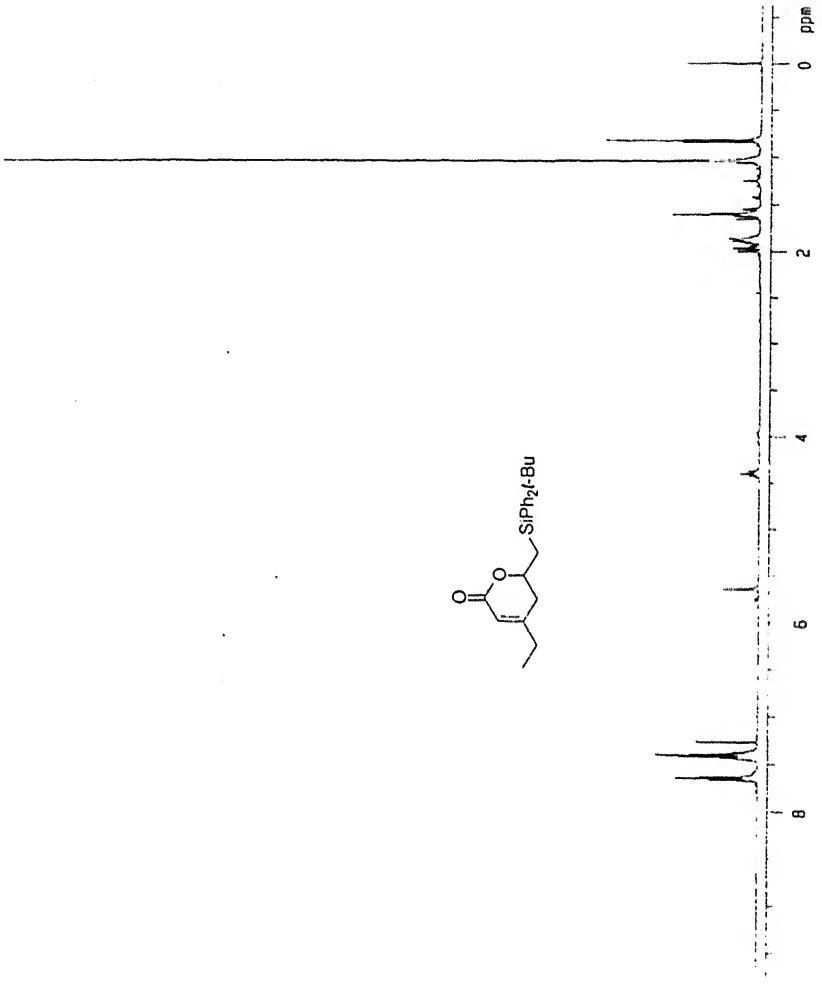


Figure 44. 400 MHz ^{1}H NMR spectrum of **138**

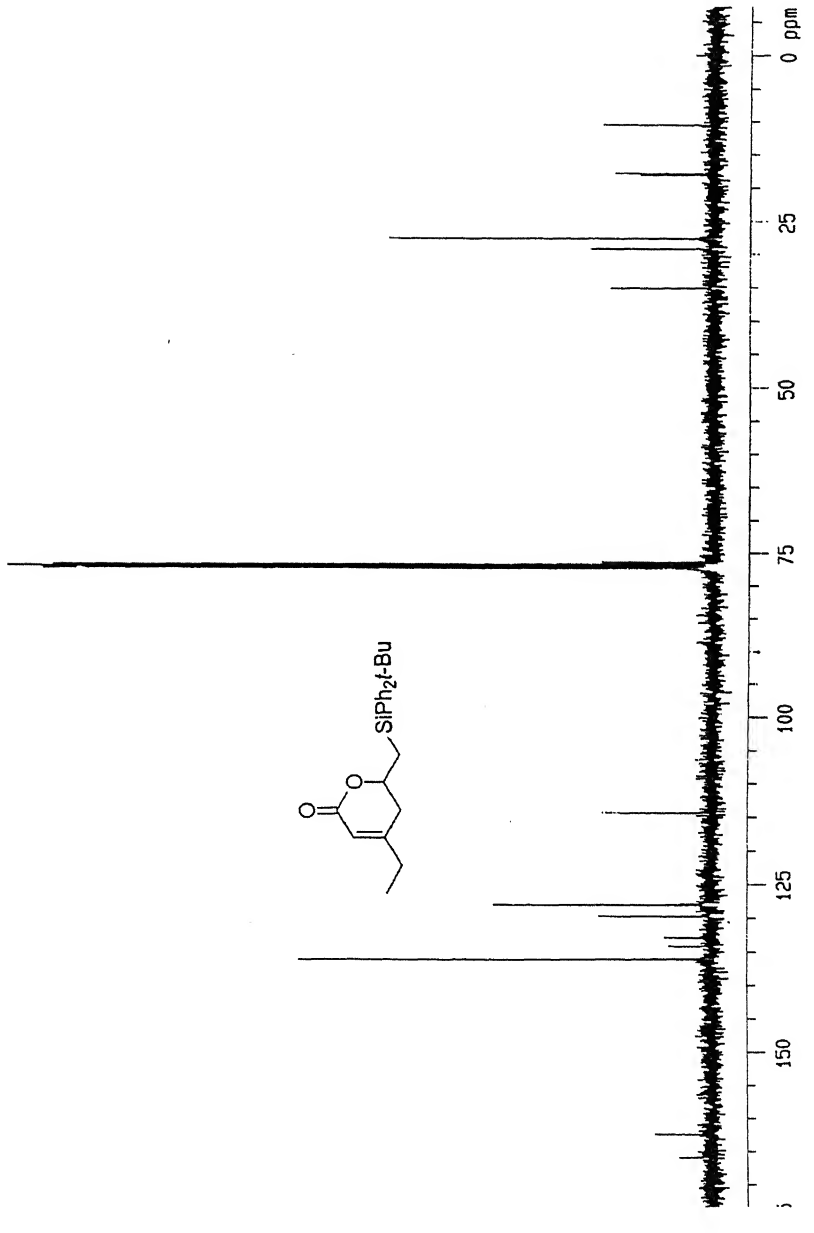


Figure 45. 100 MHz ^{13}C NMR spectrum of **138**

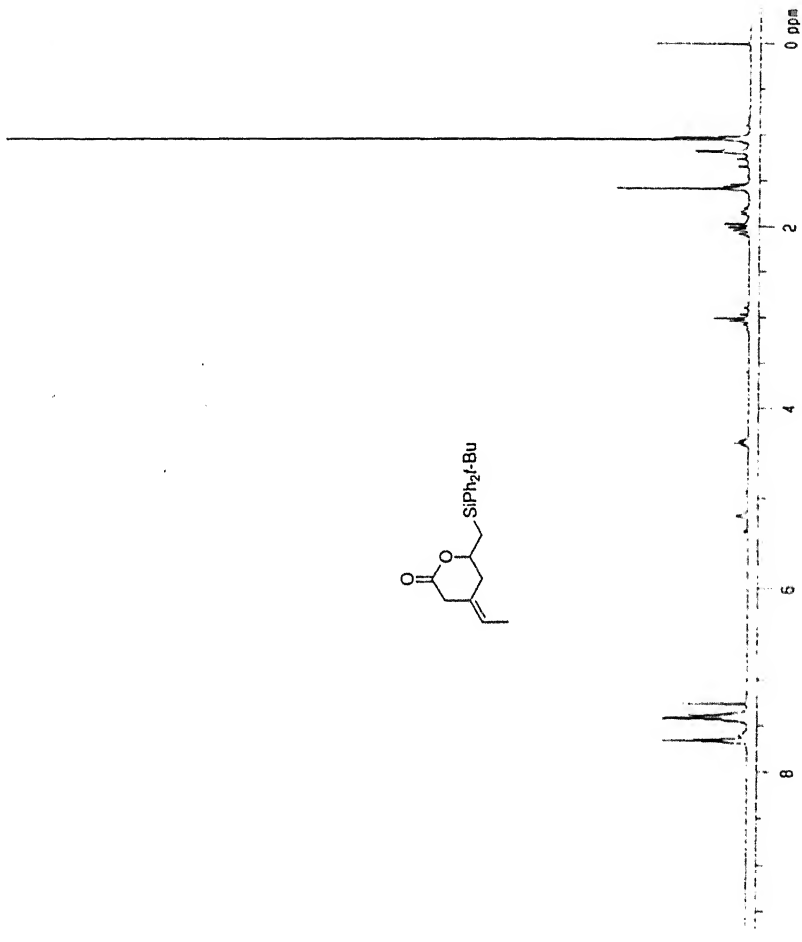


Figure 46. 400 MHz ^{1}H NMR spectrum of **140a**

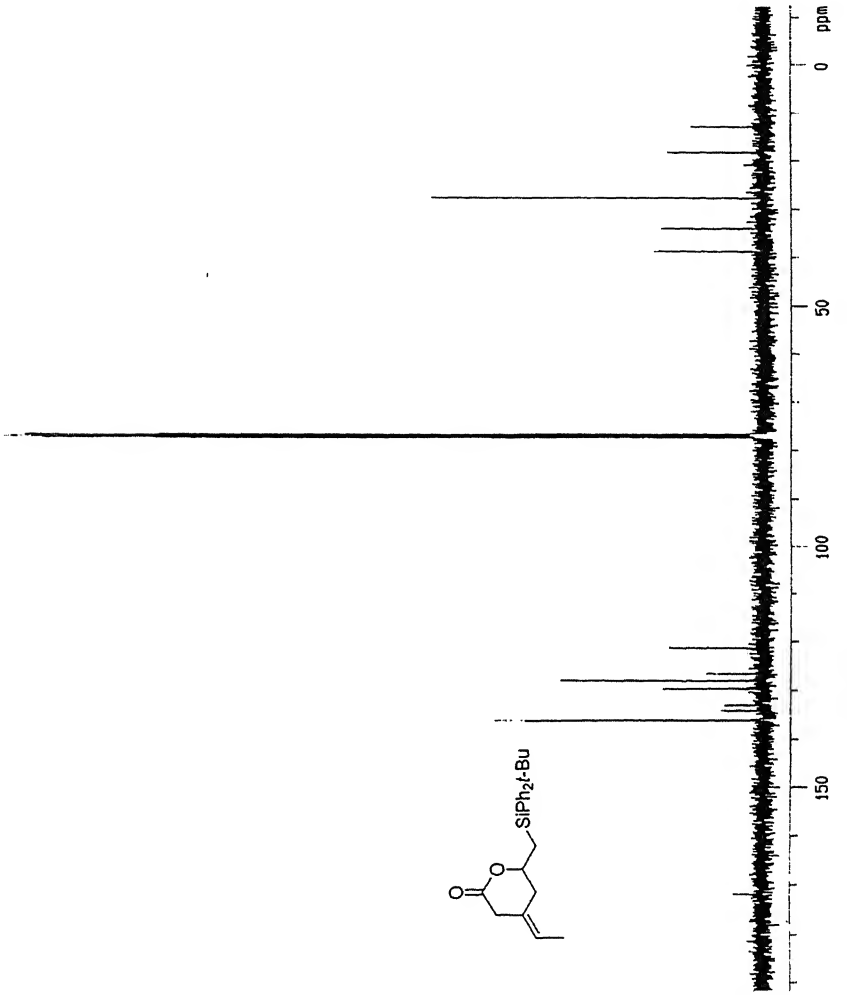


Figure 47. 100 MHz ^{13}C NMR spectrum of **140a**

Chapter 2

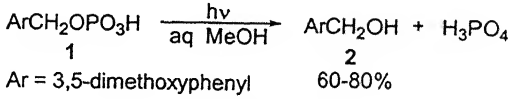
Photochemistry of Thionophosphates

2.1 Introduction

Phosphate group is one amongst the less studied functional groups by photochemists besides its primary utility as a leaving group.[1] It has one of the weakest UV-visible absorptions and thus it is generally considered as a less significant contributor to the absorption of the incident radiation by the molecules possessing this moiety. Interestingly, phosphate group is photoreactive under solvolytic and hydrolytic conditions. Moreover, the operational chromophore which absorbs the incident radiation is generally α to the phosphate group. Despite these apparent restrictions, the photochemistry of molecules containing phosphate ester function is of immense interest in the study of the functions of nucleotides and organophosphates in biological processes. A major impetus for investigating the photochemistry of phosphate esters was the desire for alternative protecting groups for the phosphate function of oligonucleotides that would involve milder protection-deprotection sequences.

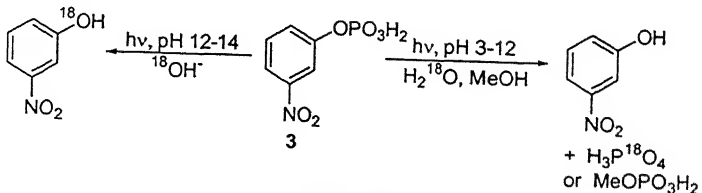
Several arylmethyl groups were found to be good protecting groups for phosphate protection. In 1970, Clark *et al.* studied the photosolvolysis of 3,5-dimethoxybenzylphosphate to obtain 3,5-dimethoxybenzyl alcohol in 60-80% yields (Scheme 1).[2] This study

constitutes one of the early works to demonstrate photo-nucleophilic substitution reaction of benzyl phosphates.



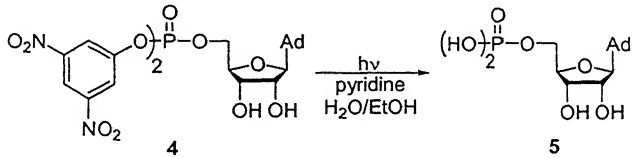
Scheme 1

During the same period, Havinga *et al.* observed the decomposition of *o*-, *m*-, and *p*-nitrophenyl phosphates that produced yellow solutions of nitrophenol on keeping their solutions in light.[3] A striking observation was the much greater reactivity of the *m*-isomer toward nucleophilic substitutions. This represents a very fine example of the unusual reversal of substituent effect in the excited state compared to the ground state reactivity. The same authors further demonstrated the involvement of short-lived singlet excited state in this S_NAr^* substitution of *m*-nitrophenyl phosphates. The mechanism of this photosolvolysis is controlled by unusual pH dependence. At higher pH (>12), attack of HO^- occurred at the *ipso* carbon of the aromatic ring. Contrary to this, attack of H_2O occurred at phosphorous at pH <12 (Scheme 2).



Scheme 2

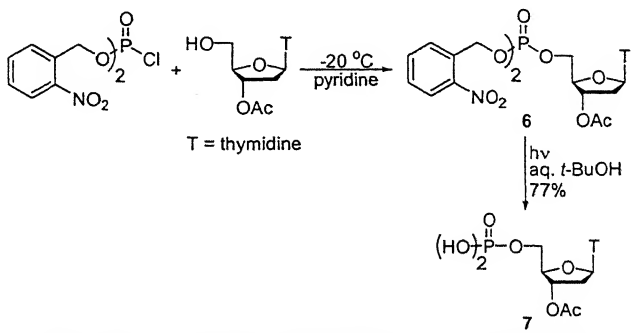
Kirby and Varvoglis exploited Havinga's results and intrduced 2,4- and 3,5-dinitrophenyl ligands as 'cage' for the protection-deprotection sequence for adenosine 5′-monophosphate (Scheme 3).[4]



4 5

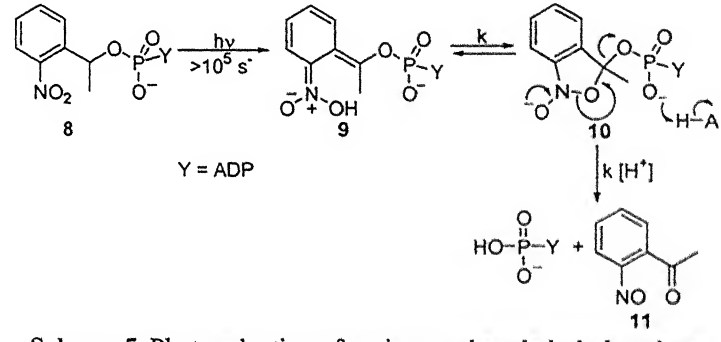
Scheme 3

In a mechanistic investigation of aryl group deprotection, Rubinstein *et al.* found *o*-nitro benzyl group as a decent ligand for nucleotide protection-deprotection process.[5] This chemistry was successfully implemented in the synthesis of thymidine 5′-monophosphate (TMP) 7 (Scheme 4) and uridine 5′-monophosphate (UMP). The formation of *o*-nitrosobenzaldehyde in the deprotection event was the only problem in the UMP synthesis as it resulted in dark colored byproducts that were difficult to remove. This problem was rectified by sequestering nitrosobenzaldehydes with insoluble polymeric hydrazide and UMP was obtained in 91% yield.



Scheme 4. Synthesis of thymidine 5′-monophosphate

In a minor modification of the ligand, Walker *et al.* introduced *o*-nitro-α-phenylethyl group as a better alternative for the simple *o*-nitrobenzyl group for two reasons.[6] First, the yields of phosphate ester formation are relatively modest, and second, the *o*-nitrosoacetophenone, a byproduct in the photodeprotection step, was quite stable to avoid the complications from the formation of unwanted byproducts. The authors also demonstrated a detailed mechanistic study of the photochemical behavior of this phosphate ester as shown in scheme 5.

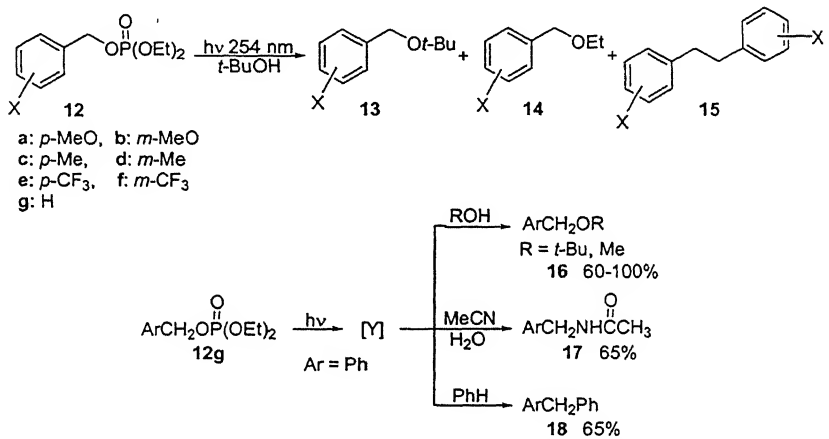


Scheme 5. Photoreduction of *o*-nitro-α-phenylethyl phosphate

The reaction involves a transient formation of *aci*-nitro intermediate **9** which absorbs at 740 nm in the UV-visible spectrum. The *aci*-nitro intermediate subsequently undergoes an intramolecular cyclization followed by ring opening to release the phosphate group under hydrolytic conditions.

Givens *et al.* have studied the photochemical behavior of a series of substituted benzyl and naphthylmethyl diethyl phosphates, giving main emphasis on the scope and the mechanism of the photo-

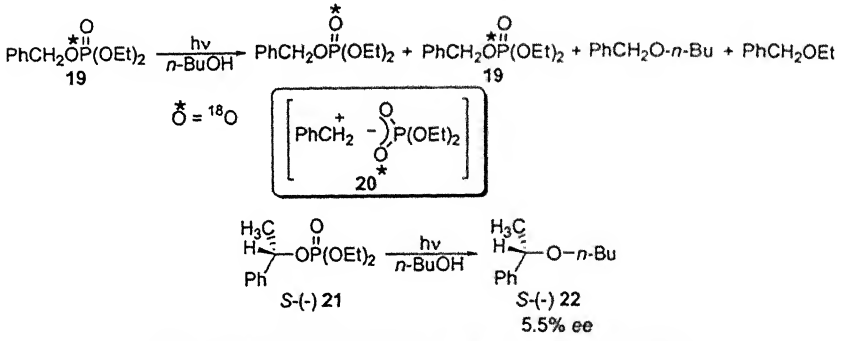
fragmentation process.[7] Irradiation of a series of benzyl and α- and β-naphthylmethyl phosphates in *tert*-butyl alcohol gave predominately the *tert*-butyl ethers **13** *via* ionic intermediates (Scheme 6). Ethyl ethers **14** and 1,2-diarylethanes **15** were also formed in minor amounts. The electrophilic character of the intermediate proposed in the above photochemical substitution reaction was proved from cation quenching reactions with moist acetonitrile and benzene.



Scheme 6. Photochemistry of benzylic phosphates

The authors have proposed the reaction to occur through an ion-pair mechanism. ^{18}O labelling, stereochemical, and substituents effects were in support of the mechanism. The ^{18}O-labelled benzylic phosphate **19** was photolysed and the recovered starting phosphate analyzed for the distribution of ^{18}O (Scheme 7). The scrambling of ^{18}O in between the benzyloxy and phosphoryl oxygens indicated the intermediate ion-pair **20** that was capable of interchanging the two

oxygen atoms. The formation of ion-pair was explicit from the efficient racimization of the chiral phosphate S-(-) **21** on photolysis.

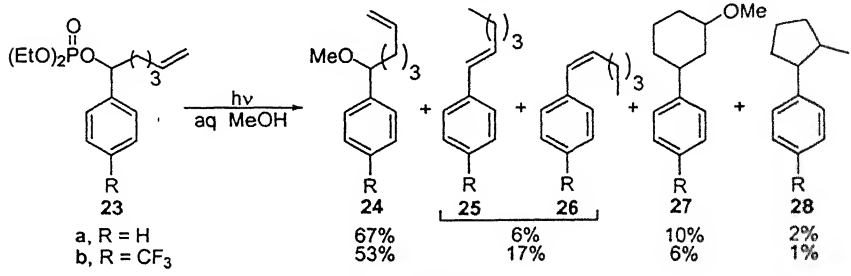


Scheme 7. Reactions favoring ion-pair mechanism

Reactions of the phosphates **12a**, **12e**, and **12g** occurred at substantially low quantum efficiencies under acetone sensitization, indicating modest reactivity of the triplet state. Quenching studies with *trans*-piperilene did not help, as there was no diminution in the efficiency of phosphate disapperance and ether appearance. These studies favored singlet state as the reactive species though the results were not fully conclusive. Hammet substituent studies were carried out with a series of substituted benzylic phosphates. The ρ value for the slope obtained from the plot of log k_r (ion-pair formation) *vs.* Hammet σ values was calculated to be –0.90. Such a high ρ value is indication for an electron-deficient center at the benzylic carbon during fragmentation.

While majority of observations supported heterolytic fragmentation, the authors designed the phosphates **23a** and **23b**, particularly, to probe the possibility of homolytic cleavage (Scheme 8).

There is a very fair chance that the initially formed radical-pair may transform into an ion-pair on electron transfer to account for the observed products.[8] In the event, it was discovered that the formation of cyclopentane products was found to be very minor. This indicated a remote propensity for homolytic cleavage.

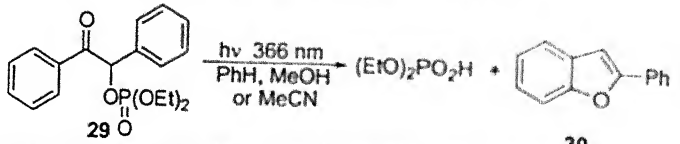


Scheme 8

The product distribution was clearly indicative of an ion-pair mechanism which also explained the 3-fold increase in the yield of the elimination products **25** and **26** when the substituent was *p*-CF_3. Being a powerful electron-withdrawing group, *p*-CF_3 enhanced the reactivity of the carbocationic intermediate by destabilizing it.

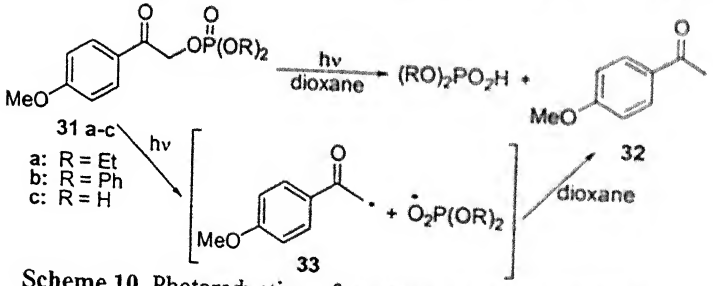
α-Keto phosphates are yet another class of phosphates that has mechanistically interesting photochemical behavior. Benzoin diethyl phosphate **29** was converted into diethyl phosphate and 2-phenylbenzo[*b*]furan **30** in nearly quantitative yield (Scheme 9).[7a] Irrespective of the polarity and the nucleophilicity of the solvent, the same product **30** was obtained from the reactions of **29** in benzene, acetonitrile, and methanol. Unlike the photosolvolysis of the benzyl and naphthylmethyl analogs, these photoreactions occured through the triplet manifold which was confirmed from quenching and sensitization

experiments.[9] The mechanism of benzofuran formation is not yet completely understood. The authors have proposed homolysis of the carbon-phosphate oxygen bond followed by a rapid electron transfer to generate an ion-pair.[9b] At this stage, the carbonyl oxygen cyclizes at the aryl ring to form the observed benzofuran derivative.



Scheme 9. Conversion of benzoin phosphate into 2-phenylbenzo[*b*]furan

Epstein *et al.* have reported on the photoreduction of *p*-methoxyphenacyl phosphates **31a-31c** in dioxane as solvent.[10] These reactions resulted in the formation of dialkyl phosphate and *p*-methoxyacetophenone. The authors concluded β-homolytic cleavage followed by hydrogen atom abstraction from dioxane by the resulting α-keto radical as the mechanism of photoreduction (Scheme 10).

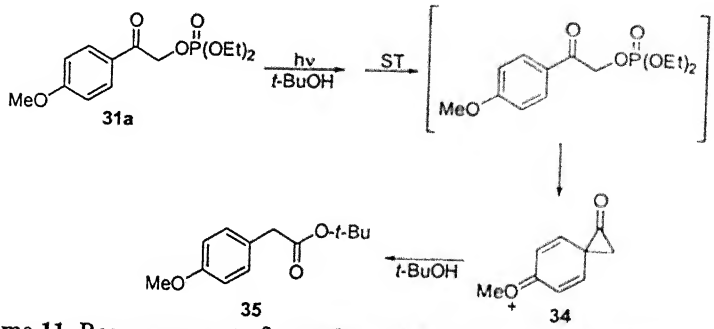


Scheme 10. Photoreduction of *p*-methoxyphenacyl phosphate

Baldwin *et al.* have studied the photochemical reactions of *p*-methoxyphenacyl phosphate, benzoin phosphate, and *o*-nitrophenylmethyl phosphate.[11] The release of the inorganic phosphate

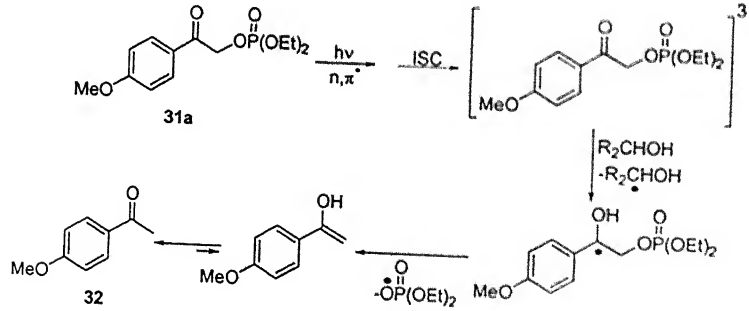
was highly efficient from benzoin phosphate in comparison to those from the other phosphates. *p*-Methoxyacetophenone was obtained in major amounts on irradiation of *p*-methoxyphenacyl phosphate in dioxane. These studies supported Epstein's mechanism of homolytic β-cleavage.

The homolytic cleavage proposed by Epstein[10] and Baldwin[11] contrasted the mechanism involved in the photochemistry of benzylic and benzoin phosphates where the primary process was proposed to be the heterolytic cleavage of the carbon-oxygen bond. This inconsistency led Givens *et al.* to reinvestigate the results of Epstein *et al.*, mainly because in solvents like dioxane, a good hydrogen atom donor, photoreduction was the major or even the exclusive pathway. They conducted photolysis of **31a** in polar solvents such as MeOH and *t*-BuOH.[9a,b] In addition to the products obtained by Epstein and by Baldwin, rearranged *tert*-butyl *p*-methoxyphenylacetate **35** was also obtained as the major product in *tert*-butyl alcohol, a solvent known to be a poor hydrogen atom donor. Likewise, in methanol, an excellent hydrogen atom donor, appreciable amount (38%) of methyl *p*-methoxyphenylacetate was obtained. The formation of the rearranged products was rationalized by the conventional neighboring *p*-anisyl participation with the developing electron-deficient α-ketocarbocation-like center (Scheme 11).



Scheme 11. Rearrangement of *p*-methoxyphenacyl monophosphate into *tert*-butyl-*p*-methoxyphenyl acetate

The formation of *p*-methoxyacetophenone was found to be suppressed by a factor of approximately 5 when the reaction was carried out in CD_3OD while it remained the same when the reaction was conducted in CH_3OD. This primary isotope effect suggested the possibility of hydrogen atom abstraction by the triplet keto phosphate (Scheme 12) which the authors proposed as an alternative to the Epstein's mechanism.



Scheme 12. Mechanism of photoreduction of **31a** proposed by Givens

2.2 Present work

2.2.1 Objectives

The photochemistry of phosphate esters, $ROP(O)(OEt)_2$, has been shown to involve an ionic dissociation-recombination pathways. Although the heterolytic cleavage is the predominant pathway, the formation of small amounts of radical-derived products indicates the involvement of homolytic cleavage as well. A study of homolytic *vs.* heterolytic cleavage of the benzylic derivatives as a function of substituents and solvents was undertaken by different groups[12] to favor homolytic cleavage with carboxylic esters, methylsulfone, and halides as the benzylic substituents. We were motivated to study the photochemistry of thionophosphates, $ROP(S)(OEt)_2$, because the replacement of the phosphoryl oxygen with sulfur was expected to promote homolytic cleavage under non-solvolytic conditions for its good radical-stabilizing ability. The resulting radicals may then be effectively used for further synthetic manipulations under a concept that is similar to that of Barton decarboxylation of thiohydroxamic esters.[13]

2.2.2 Starting materials

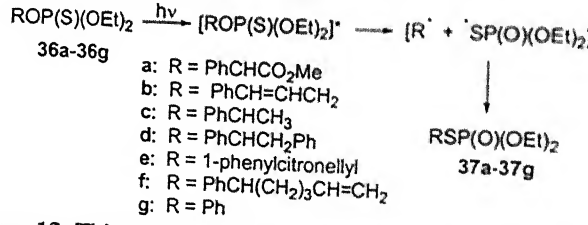
The thionophosphates were derived from methyl mandelate, 1-phenyl-5-hexenol, cinnamyl alcohol, 1-phenylethanol, 1,2-diphenylethanol, 1-pheylcitronellol, *trans*-4-*tert*-butylcyclohexanol, (*E*)-2-buten-1-ol, 1-phenyl-2-propanol and 1-(2-phenylcyclopropyl)ethanol on reaction of their sodium salts with diethyl chlorothiophosphate at 0-25 °C. It is important to note that the

earlier method that employed pyridine as base for the preparation of phosphates was fully ineffective. [7b]

2.2.3 Results and discussion

2.2.3.1 Isomerization of thionophosphates into thiolophosphates

Irradiation in CH_3CN resulted in a smooth transformation of the thionophosphates **36a-36g** into the related thiolophosphates **37a-37g** (Scheme 13). Some 65-70% of the initial thionophosphate had reacted. The thiolophosphates were separated readily from the unchanged thionophosphates by chromatographic techniques including radial chromatography over silica gel. Except for the cinnamyl thionophosphate, all other thionophosphates were stable to thermal conditions[14] and silica gel chromatography. Cinnamyl thionophosphate isomerized[15] on chromatography over silica gel to furnish the same product mixture as that produced from irradiation (*vide infra*). However, the ratio of the isomeric products was different from that produced from the photochemical reaction.



Scheme 13. Thionophosphate-thiolophosphate photoisomerization

The species **38** and **39** (Figure 1) were also formed in small amounts from the reaction of methyl mandelate-derived thionophosphate. The corresponding thiolophosphate, however, was still the major product. While the structure of **38** was confirmed from

spectroscopic characteristics, exact mass measurement analysis, and comparison with literature data,[16] the structure of **39** was secured from a single crystal X-ray structure determination (Figure 2).[17] Cinnamyl thionophosphate underwent transformation, both without and with allylic shift, to furnish **37bi** and **37bii**, respectively. The efficacies of the rearrangements of 1-phenylethanol and 1-phenylcitronellol derivatives were somewhat low in comparison to those of methyl mandelate and cinnamyl alcohol derivatives and longer irradiation (30 min) was required for ≥65% conversion. The results are collected in Table 1.

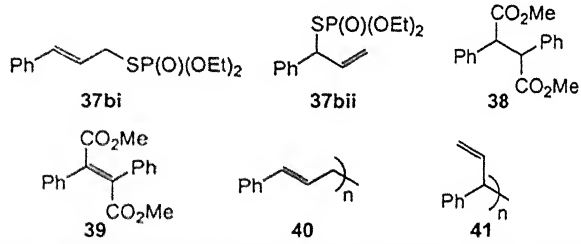


Figure 1. Structures of products obtained from some photoreactions

1-Phenyl-5-hexenyl thionophosphate underwent both rearrangement to the corresponding thiolophosphate and elimination to generate a mixture of (*Z*)- and (*E*)-1-phenyl-1,5-hexadienes[18] in almost equal amounts. 1,2-Diphenylethyl thionophosphate reacted similarly to give the corresponding thiolophosphate and a mixture of (*Z*)- and (*E*)-stilbenes in almost equal amounts.

Table 1. Results of selected thionophosphate –thiolophosphate photoisomerizations

Thionophosphate from	Irradiation time (min)	Conversion (%)
Methyl mandelate **36a**	15	70
Cinnamyl alcohol **36b**	15	68
1-Phenylethanol **36c**	30	65
1,2-Diphenylethanol **36d**	30	67
1-Phenylcitronellol **36e**	30	65
1-Phenyl-5-hexenol **36f**	30	65
Benzyl alcohol **36g**	30	65
4-*tert*-Butylcyclohexanol **36h**	120	NR
1-Phenyl-2-propanol **36i**	120	NR
trans-2-Butenol **36j**	120	NR

NR = no reaction. In all the cases, the isolated yield of the thiolophosphate based on the reacted thionophosphate was 90% and above.

The chemistry of the thionophosphates **36h-36j** prepared, respectively, from *trans*-4-*tert*-butylcyclohexanol, 1-phenyl-2-propanol and *trans*-2-buten-1-ol were studied to understand the role of the aromatic ring. There was no reaction even after irradiation for 120 min. It appears, therefore, that the light is absorbed first by the aromatic ring and then transmitted, in some way, to the P=S function. The failure of the thionophosphate **36i** derived from 1-phenyl-2-propanol to undergo the thiono-thiolo isomerization suggests further that the aromatic chromophore must necessarily be present at the carbinol carbon for a meaningful reaction to take place.

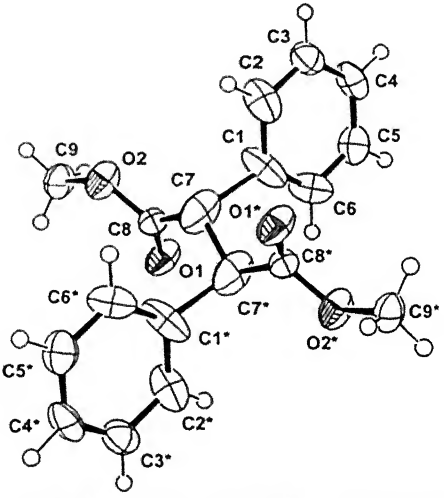


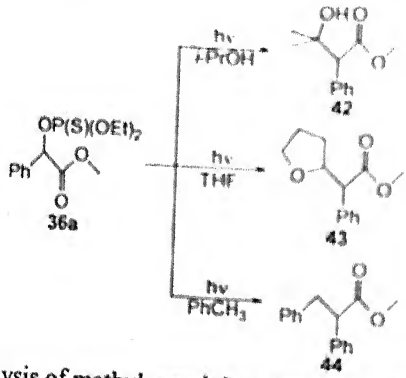
Figure 2. Ortep drawing of **39**. Selected crystal data: M = 296.32, monoclinic, a = 5.845 (5), b = 17.134 (4), c = 7.935(7) Å, β = 107.54(6) °,Z = 2, D_c = 1.299 g cm^{-3}, μ = 0.91 cm^{-1}. R = 0.076 and R_w = 0.051. C7-C7* = 1.402(14) Å, C8-O1 = 1.190(7) Å, C8-C7-C7* = 111.0(9)°, O1-C8-C7 = 125.9(7)°, O1-C8-C7-C7* = -35.9(14)°, C6-C1-C7-C7* = 46.7(11)°, O2-C8-C7-C7* = 149.8(10)°, O1-C8-O2-C9 = 0.8(11)°, C7-C8-O2-C9 = 175.2(6)°.

2.2.3.2 Irradiation in *i*-PrOH

In view of the formation of **38** and **39** above, radical pathway was considered to be more appropriate than the ionic dissociation-recombination alternative. This led us to study the reactions of selected thionophosphates in isopropanol which is a good hydrogen atom donor under radical conditions. It was expected to quench the phosphate radical derived from the thionophosphate to generate $(RO)_2P(O)SH$, or, a derivative thereof, and itself combine with the benzyl radical to result in a C-C bond formation.

In the event, irradiation of a solution of methyl mandelate-derived thionophosphate in *i*-PrOH for 30 min furnished the β-hydroxy

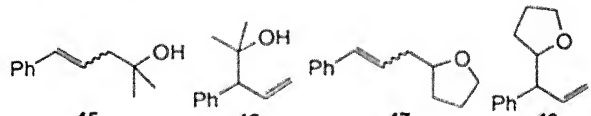
ester **42** as the sole product; none of the cation-quenched product methyl phenylacetate was formed (Scheme 14). This experiment demonstrated clearly that the carbocationic intermediate was not formed. This is to be contrasted with the results from the irradiation of $ArCH_2OP(O)(OEt)_2$ in solvents such as alcohols (ROH), moist CH_3CN, and benzene when $ArCH_2OR$, $ArCH_2NHCOMe$, and $ArCH_2C_6H_5$, respectively, constituted the predominant products that arose from the reaction of $ArCH_2^{\bullet}$ with the solvent molecules. It is significant to note that we have never isolated any amide-like products from the reactions in CH_3CN. Likewise, C_6H_5-incorporated products were also not isolated from the reactions in benzene.



Scheme 14. Photolysis of methyl mandelate derived thionophosphate **36a** in different hydrogen atom donating solvents

Cinnamyl thionophosphate reacted in *i*-PrOH to furnish the dimers **40** and **41** (5%, combined), the isomeric thiolophosphates **37bi** and **37bii** (40%, combined), and **45** (25%). The product **46** (Figure 3) that is isomeric to **45** was not formed. The reaction, therefore, had proceeded with very high regioselectivity. The formation of more *cis*-

isomer than the corresponding *trans*-isomer of **45** must be a consequence of photo-induced olefin isomerization. The 1,2-diphenylethyl thionophosphate underwent smooth elimination to furnish a mixture of (*Z*)- and (*E*)-stilbenes; *i*-PrOH-incorporated product was not formed. 1-phenylethanol furnished only the corresponding thiolophosphate.



45 **46** **47** **48**

Figure 3. Products thionophosphate **36b** with *i*-PrOH and THF

2.2.3.3 Irradiations in THF and toluene

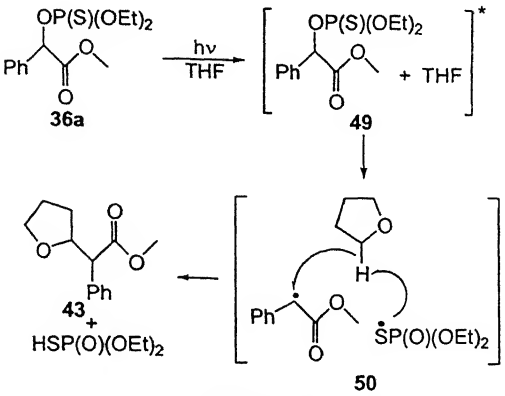
The generation of radical species from methyl mandelate-derived thionophosphate was confirmed further by conducting the irradiation in non-alcoholic solvents such as THF and toluene. The methyl mandelate derivative furnished **43**[19] and **44**[20] from the reactions in THF and toluene, respectively (Scheme 14). The reaction in THF was more efficient than the reaction in toluene. Cinnamyl thionophosphate furnished an inseparable mixture of products **47** and **48** (20%), **48** being minor compared to **47** (Figure 3). The *E*- and *Z*-olefin geometries in **47** were determined from the ^{1}H coupling constants of the vinylic hydrogens that were 15.6 and 11.7 Hz, respectively. Here also, the *cis*-isomer was found to be major (*cis*:*trans*=3.4:1). The dimeric species **40** and **41** (5%, combined) and the thiolophosphates **37bi** and **37bii** (45%, combined) were also

formed. The results of the reactions of selected thionophosphates are collected in Table 2.

Table 2. Results of the reactions of selected thionophosphates with *i*-PrOH, THF, and toluene

Thionophosphate from	Solvent	Irradiation time (min)	Conversion (%)	Product (%)
Methyl mandelate **36a**	*i*-PrOH	30	70	90
Methyl mandelate **36a**	THF	30	75	90
Methyl mandelate **36a**	Toluene	30	50	85
Cinnamyl alcohol **36b**	*i*-PrOH	120	89	25
Cinnamyl alcohol **36b**	THF	120	91	20

The reactions in THF may be considered to proceed as shown in Scheme 15. It is the sulfur radical, and not the carbon radical, that abstracts a hydrogen atom from THF. In support of this, we have never isolated any methyl α-phenylacetate that would be formed if the carbon radical were to abstract a hydrogen atom from THF. The products from the self-couplings of tetrahydrofuran-2-yl radical and the carbon centered radical of methyl α-phenylacetate were not formed either. The cross-coupling, therefore, is greatly favored over the self-coupling. This has some bearing on the reaction mechanism. The THF molecule that has diffused into the exciplex **49/50** is probably readily available for hydrogen atom abstraction by the sulfur radical. This is then followed by a fast capture of the so-generated 2-tetrahydrofuranyl radical by a benzyl radical.



Scheme 15

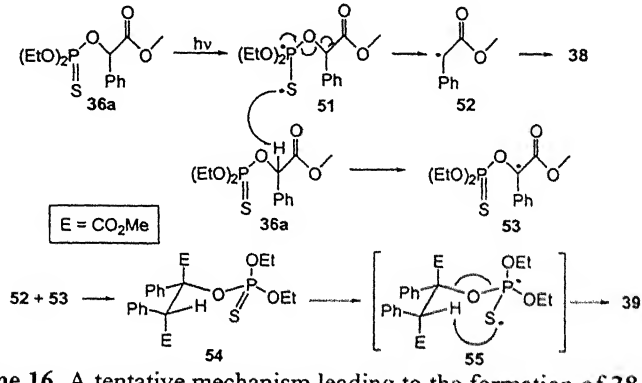
2.2.3.4 Further evidence for radical participation

Dioxygen is an effective quench for radical. A 10 mM CH_3CN solution (30 mL) of methyl mandelate-derived thionophosphate was bubbled with dioxygen for 30 min and then irradiated for 15 min. ^1H NMR analysis indicated 8:1 ratio of thiono- and thiolophosphate as against a ratio of 3.5:1 when the dioxygen was replaced by argon under otherwise identical conditions. The low thiono-thiolo conversion in the presence of dioxygen indicates involvement of radical(s).

In yet another experiment, a 30 mL CH_3CN solution of methyl mandelate-derived thionophosphate and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), 10 mM in each, was degassed by bubbling with argon for 30 min and then irradiated for 15 min. Chromatographic purification allowed isolatation of the product of quench of the benzyl radical of methyl α-phenylacetate with TEMPO. This experiment confirmed the participation of radicals beyond doubts.

2.2.3.5 A tentative mechanistic rationale for the formation of the species 38 and 39

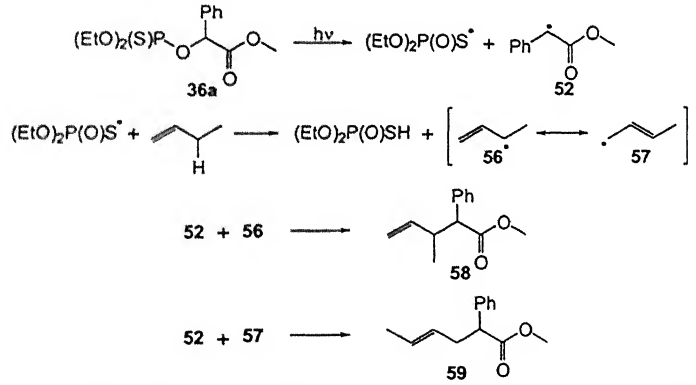
With the participation of radical species confirmed, we can now speculate on the events in the formation of **38** and **39** as in Scheme 16. The benzylic hydrogen in methyl mandelate-derived thionophosphate is highly reactive. The carbon radical **53**, formed from its abstraction in an intermolecular process *via* the diradical **51** as shown, is stable. The combination of radicals **52** and **53** would give yet another thionophosphate **54** which would react through a six-centered cyclic TS **55** involving a hydrogen atom transfer to deliver **39**. The possibility of this step is evident from the fact that the thionophosphate **36d** derived from 1,2-diphenylethanol, a structural analog of **54** but without the ester functions, gave stilbenes in considerable amounts. The self-coupling of the radical **52** generates **38**. The product of self-coupling of **53** was not formed. This may be due to the large steric crowding that would develop around the carbon-carbon bond that would form from such a reaction.



Scheme 16. A tentative mechanism leading to the formation of **38** and **39**

2.2.3.6 Allylic benzylation of alkenes

The demonstrated ability of sulfur radicals to abstract a hydrogen atom from *i*-PrOH, THF, and toluene raised the possibility of using olefins as possible hydrogen atom donors. The abstraction of a hydrogen atom from an allylic carbon will generate a radical that could, in principle, combine with the earlier formed benzyl radical in a subsequent step to generate a product of net allylic benzylation. This concept is illustrated in Scheme 17 with 1-butene as the representative example. The first formed allylic radical **56** and its resonance isomer **57** will be expected to combine with the radical **52** to generate a mixture of **58** and **59**, respectively.



Scheme 17. The different possibilities in the allylic benzylation of but-1-ene

The above premise was put to experimental test and we investigated the irradiation of selected thionophosphates and olefins such as cyclopentene, cyclohexene, 1-methylcyclohexene, cyclooctene, 1,5-cyclooctadiene and 1-decene in CH_3CN. It was gratifying indeed to discover that the reactions proceeded just as expected. From all these reactions, the dimeric materials **38** and **39** and the corresponding

thoilophosphates were also formed in small to significant amounts. The results of the reactions of different thionophosphates **36a-36c** and **36g** with various olefins are collected in Table 3.

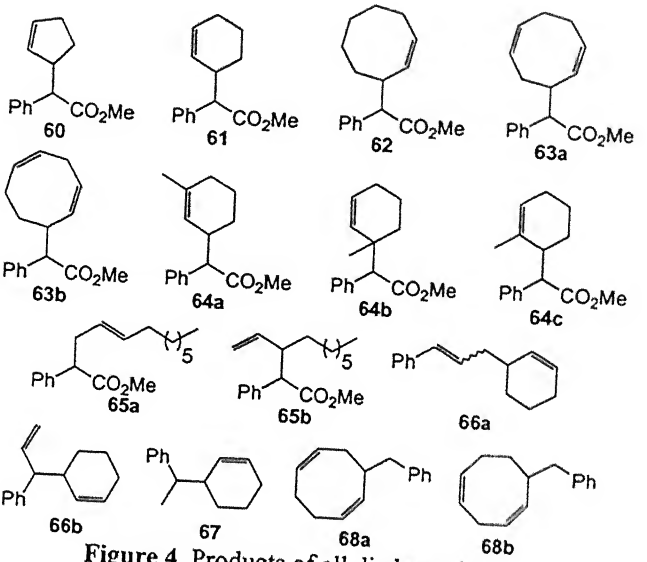
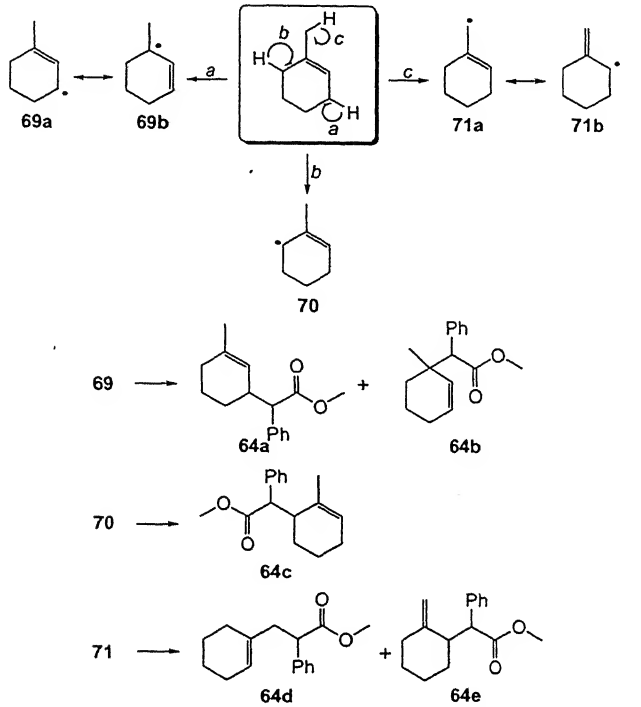


Figure 4. Products of allylic benzylation

Table 3. Results of allylic benzylation of selected alkenes with thionophosphates **36a-36c** and **36g**

C-O	Olefin	Product distribution (%)		
		Benzylation	Dimer(s)	C-O→C-S
36a	Cyclopentene	38.2 (**60**)	14.4	17.8
36a	Cyclohexene	32.0 (**61**)	13.2	23.0
36a	Cyclooctene	34.4 (**62**)	12.4	30.8
36a	1,5-Cyclooctadiene	33.0 (**63**)	16.6	20.2
36a	1-Methylcyclohexene	38.4 (**64**)	16.2	18.4
36a	1-Decene	29.7 (**65**)	17.5	23.0
36b	Cyclohexene	31.8 (**66**)	09.5	46.2
36c	Cyclohexene	25.1 (**67**)	-----	42.5
36g	1,5-Cyclooctadiene	24.5 (**68**)	14.0	21.0

C-O = Thionophosphate, C-S = Thiolophosphate.
The yields of all the products are based on the reacted thionophosphate (conversion: **36a**, 70-75%; **36b**, 94%; **36c**, 55%; **36g**, 59%).



Scheme 18. Allylic benzylation of 1-methylcyclohex-1-ene

1-Methylcyclohexene could, in principle, furnish a total of five regioisomers, **64a-64e** (Scheme 18). The regioisomers **64a** and **64b** represent the products derived from the radical **69**. The regioisomer **64c** will be derived from the radical **70**. Finally, the regioisomers **64d** and **64e** will be formed from the radical **71**. Of these five possible regioisomers, only the isomers **64a-64c** were formed. The isomer **64b** was separated from the mixture. The isomers **64a** and **64c** were inseparable from each other even by chromatography over $AgNO_3$-impregnated silica gel. The ratio **(64a+64c):64b** was 4:1. Clearly, the

radical coupling at the secondary carbons was 4 times faster than the coupling at the tertiary carbon. Hydrogen abstraction did not occur at the methyl group and, thus, the regioisomers **64d** and **64e** were not formed.

1-Decene reacted with methyl mandelate-derived thionophosphate and furnished an inseparable 1.5:1 mixture of **65a** and **65b** (Figure 4) that emanated from benzylations at C-1 and C-3, respectively. The first formed allylic radical was resonance stabilized and it reacted through both the ends.

The cinnamyl thionophosphate furnished a mixture of (*E*)- and (*Z*)-3-(2-cyclohexenyl)-1-phenylpropene, **66a**, and a diastereomeric mixture of 3-(2-cyclohexenyl)-3-phenylpropene, **66b**, on reaction with cyclohexene. The *cis*:*trans* ratio of **66a** was estimated as ~1:1 from the ^{1}H integrals of the olefinic hydrogens at C-1. The 1:1 diastereomeric mixture of **66b** was separated into its components by radial chromatography. The product from 1-phenylethanyl thionophosphate and cyclohexene was a 1:1 mixture of the diastereomeric 1-(2-cyclohexenyl)-1-phenylethane, **67**.

The reaction of 1,5-cyclooctadiene with **36a** was likely to give two diastereomeric products, **63a** and **63b**. The structure assignment as to whether the product was **63a** or **63b** or a mixture of both was difficult due to the diastereomeric nature of the products. To resolve this problem indirectly, we chose to eliminate the diastereomeric component to simplify product composition and, hence, irradiated 1,5-cyclooctadiene and benzyl thionophosphate **36g** under identical

conditions to isolate a mixture of two compounds along with a small amount of 1,2-diphenylethane. Fortunately, these two compounds could be separated easily by column chromatography over $AgNO_3$-impregnated silica gel and they were characterized as **68a** and **68b** from their individual spectroscopic data including 2D ^1H NMR. The product from the allylic shift was, therefore, formed. In keeping with this, we conclude that a mixture of **63a** and **63b** was formed from the reaction of 1,5-cyclooctadiene with methyl mandelate-derived thionophosphate.

2.2.3.7 Reactions with allyl bromides

A variation of the allylic benzylation of alkenes could be the addition of one of the radicals derived from thionophosphates to alkenes containing radical leaving groups at the allylic position. Zard *et al.* have recently demonstrated a conceptually similar intermolecular radical allylation[21] and vinylation[22] of dithiocarbonates.

We have treated selected thionophosphates **36a-36c** with different allyl bromides for 1 h under standard photolytic conditions. To our surprise, only the sulfur radical had added to the double bond and resulted in the formation of the corresponding allyl thiolophosphate (Figure 5). The products from the addition of the benzylic radicals were not observed. From the reaction of methyl mandelate-derived thionophosphate, considerable amounts of methyl α-bromo-α-phenylacetate were also isolated. However, similar benzylic bromides were not obtained from the reactions involving thionophosphates derived from cinnamyl alcohol and 1-phenyl ethanol. The reason this discrepancy is not understood yet. The yield of the thiolophosphate **75**

from the reaction of 3-bromo-2-carbethoxypropene was generally high. This may be due to the electron withdrawing ester function which favored the nucleophilic radical addition of the sulfur-centered radical. Although the thionophosphate **36b** derived from cinnamyl alcohol reacted well, the yields of allyl thiolophosphates were poor. From all the reactions, considerable amounts of the corresponding thiolophosphates **37a-37c** were also isolated.

An important observation from the present radical additions is that the radical displacement appeared to have occurred without the migration of double bond. For instance, the actual product from the reaction of **36a** with geranyl bromide was **74**. Likewise, when the thionophosphate **36b** was treated with crotyl bromide, **76a**[15b] was the major product as a mixture of *cis*- and *trans*-isomers. The expected product **76b** was formed in only trace amounts.

In order to know the actual mechanism involved in the formation of **74** and **76a**, we carried out the photoreaction of **36b** with crotyl bromide for 15 min. ^{1}H NMR of the crude reaction mixture revealed that **76b** had formed 1.7 times more than **76a**. In a separate experiment, a 5.5:1 mixture[23] of **76b** and the *trans*-isomer of **76a** was subjected to the standard photolysis conditions for 1 h to note that almost all of **76b** was converted into **76a**, the final **76b**:**76a** was 1:25. These experiments clearly indicate that the primary product of the reaction was **76b** which was subsequently transformed rapidly into **76a**. A similar argument is applicable to explain the formation of **74** from geranyl bromide. The involvement of radicals was also supported by

the formation of molecular bromine. A portion of the reaction mixture from the reaction of **36b** with allyl bromide was treated with a saturated aq solution of sodium thiosulfate. Substantial fainting of the brown color of reaction mixture indicated the formation of molecular bromine. To our surprise, similar reactions did not take place with allyl chlorides and allyl esters. The results are collected in Table 4.

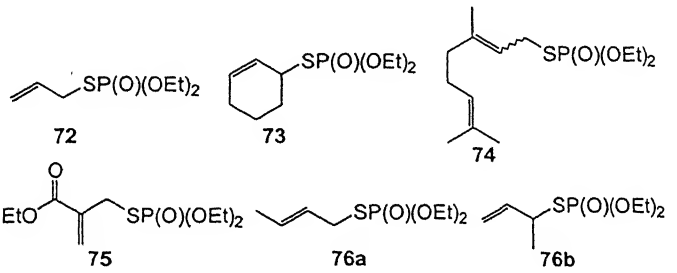


Figure 5. Products of reactions between thionophosphates and allyl bromides

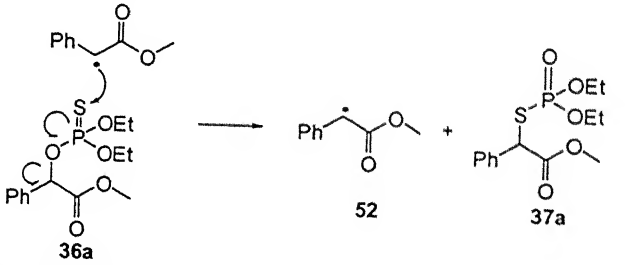
Table 4. Results of the reactions between selected thionophosphates and allylbromides

C-O	Allyl bromide	Product distribution (%)		Conversion (%)
		Allyl thiolophosphate	C-O→C-S	
36a	Allyl bromide	51 (**72**)	41 (**37a**)	35
36a	3-Bromocyclohexene	35 (**73**)	41 (**37a**)	34
36a	Geranyl bromide	33 (**74**)	39 (**37a**)	30
36a	3-Bromo-2-ethoxy-carbonyl propene	64 (**75**)	31 (**37a**)	34
36b	Allyl bromide	23 (**72**)	37 (**37b**)	91
36b	3-Bromocyclohexene	20 (**73**)	40 (**37b**)	93
36b	Crotyl bromide	15 (**76**)	36 (**37b**)	93
36c	3-Bromo-2-ethoxy-carbonyl propene	58 (**75**)	29 (**37c**)	67

C-O = Thionophosphate, C-S = Thiolophosphate.
The yields of all the products are based on the reacted thionophosphates.

2.2.3.8 Evidence in support of the non-chain radical protocol

The thionophosphate-thiolophosphate transformation proceeds in a non-chain radical fashion. This was demonstrated using methyl mandelate-derived thionophosphate as substrate. If the reaction were to proceed in a chain fashion, one will expect the carbon radical **52** to add to the sulfur across P=S and bring about further cleavage as shown in Scheme 19 to give the desired thiolophosphate with regeneration of the radical **52**. The crucial step in the design of such a radical chain is the ability of a benzylic radical to add to P=S. Though such radical additions to thione functions are implicated in the literature,[24] we discover below that this is not so in as much as the addition to P=S in a thionophosphates is concerned.



Scheme 19. The requirement(s) of the radical-chain process for the thionophosphate-thiolophosphate isomerization

A solution of hexabutylditin (2.5 mol%) in toluene was added slowly to a refluxing solution of methyl mandelate derived thionophosphate and benzyl bromide (5 mol%) in toluene. The *in situ*-generated benzyl radical from the reaction of tributyltin radical and benzyl bromide was expected to initiate the process by adding to P=S and, thus, bring about the desired overall change. Product analysis

indicated that while the thionophosphate was still present, all the benzyl bromide had been consumed. Clearly, the benzyl radical that was formed from benzyl bromide on reaction with tributyltin radical did not add to P=S. To reconfirm this finding, the following experiment was designed.

A solution of Bu_3SnH (1.2 equiv) in benzene was added slowly with the help of a syringe pump to a mixture of methyl mandelate-derived thionophosphate **36a** and benzyl bromide (1.0 equiv) at reflux. The benzyl bromide had apparently reduced to toluene as it was altogether absent in the mixture and the thionophosphate was recovered quantitatively. The benzyl radical, therefore, did not add to P=S. The tributyltin radical did not add to P=S either. This was confirmed further from a separate experiment in which a benzene solution of methyl mandelate-derived thionophosphate, Bu_3SnH (1.2 equiv) and a catalytic amount of azobisisobutyronitrile (AIBN) was refluxed for 2 h. The thionophosphate was recovered quantitatively. This last experiment was performed on 1-phenylcitronellyl thionophosphate as well, when, again, no reaction took place and the thionophosphate was recovered quantitatively.

The above observations established clearly that neither a carbon radical nor a tin radical added to P=S of thionophosphates. This being so, the transformation of a thionophosphate into the corresponding thiolophosphate could only be a non-chain radical process.

To confirm further the above non-chain protocol, we irradiated a 10 mM solution of methyl mandelate-derived thionophosphate in CH_3CN for 3 min to initiate the chain process, if any, and then waited for 12 min before the solvent was removed. The thiono-thiolo ratio was determined to be 67:1, which indicated very little conversion. The above ratio is far from 3.5:1 ratio that was observed on irradiation for 15 min. The low conversion on shorter irradiation can be explained only by the participation of a non-chain protocol. With a chain protocol, both the reactions will be expected to exhibit similar conversions.

2.2.3.9 Attempts at the cleavage of cyclopropane rings

The successful experiments with cinnamyl thionophosphate led us to explore the chemistry of cyclopropylmethanol derivatives as well. This was largely due to the understanding that a cyclopropane ring is similar to an olefin. In the event, we irradiated 77 (Figure 6) in CH_3CN and noted absolutely no reaction. This shows the significance of a true π-bond over a cyclopropane ring system; the ring apparently does not allow the transfer of energy absorbed by the aromatic unit to the thionophosphate function.

The above failure is not too difficult to understand. The transmittance of energy from the aromatic unit to the thionophosphate function across an olefinic linkage is made simple due to all-parallel nature of the p orbitals in the aromatic ring system, the two p orbitals of the olefin tether and the C-O bond axis in the thionophosphate function. In the cyclopropane derivative, if the p orbitals of the aromatic ring system are parallel to the adjacent cyclopropane carbon-carbon bond

axis, they are near orthogonal to the cyclopropane carbon-carbon bond axis at the carbinol-bearing carbon. This is likely to break the flow of energy from the aromatic core to the thionophosphate function. The transfer of energy, therefore, takes place through the bonds and not through space. This hypothesis explains the failure of 1-phenyl-2-propanyl thionophosphate to undergo isomerization to the corrposponding thiolophosphate (*vide supra*).

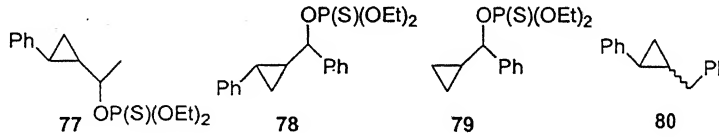
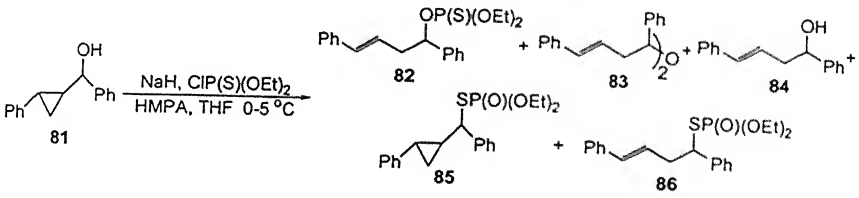


Figure 6

We considered to overcome the above difficulty by substituting a phenyl group on the carbinol carbon itself and, thus, studying the thionophosphate **78**. However, the preparation of **78** from the corresponding alcohol **81** was difficult. We isolated a host of products, **82-86**, but not the expected thionophosphate **78** from the employment of our standard conditions for its formation (Scheme 20). The formation of the products **82-86** can be explained from a combination of events such as (a) ionization leading to the formation of a cyclopropylmethyl cation, (b) cleavage of the cyclopropane ring in this cation that leads to the formation of yet another cation, and (c) the quenching of the rearranged cation by the phosphate ion through both oxygen and sulfur. The species **78**, therefore, is too unstable under the thionophosphate-forming reaction conditions to allow its isolation. The all-*E*-**82-84** and

86 show that the cyclopropane ring cleaved with very high stereoselectivity.



Scheme 20

The alcohols corresponding to the thionophosphates **77** and **78** were prepared from $NaBH_4$ reduction of the corresponding ketones which, in turn, were prepared from the corresponding α,β-unsaturated ketones following Corey's cyclopropanation method.[25]

In attempts to suppress or even stop the above rapid ionization, we also considered studying the substrate **79** that lacks the phenyl substituent on the cyclopropane ring. However, the precursor alcohol could not be prepared from the attempted cyclopropanation of vinylbenzyl alcohol under the Simmons-Smith conditions (CH_2I_2, Zn/Cu, Et_2O, reflux, 2 h). Other methods of cyclopropanation were not attempted.

Finally, in our attempts to generate a cyclopropylmethyl radical via hydrogen atom abstraction to effect the cleavage of the ring and its further quench by a carbon radical, we irradiated a mixture of methyl mandelate thionophosphate and **80** (*cis/trans* mixture) in CH_3CN. Only the thiono-thiolo isomerization was observed and the substrate **80** was recovered unchanged. This result is surprising particularly because methyl mandelate-derived thionophosphate had been found by us (*vide*

supra) to react with toluene. It just might be that the phosphate radical quenched the carbon radical faster than it could abstract a hydrogen atom from **80**.

2.3 Conclusions

Thionophosphates were conveniently isomerized into the corresponding thiolophosphates under photochemical conditions. Aromatic chromophore is needed at the carbinol carbon for the reaction to take place. The isomerization followed exclusively a non-chain radical pathway. The reactions in *i*-PrOH and THF constitute convenient protocols for the benzylation of those substrates. The irradiation of a thiononphosphate and an olefin in CH_3CN leads readily to an allylic benzylation of the latter. Allyl bromides gave the corresponding allyl thiolophosphates on irradiation with a benzylic thionophosphate. All these reactions are, however, limited to alcohols that are either benzylic or vinologously benzylic. The light absorbed by the aromatic core is transmitted to the thionophosphate function through the bonds that trigger the observed transformations. The study of thionophosphates prepared from the alcohols on reaction with diphenyl chlorothiophosphate turns out to be a distinct possibility for future investigations.

2.4 Experimental

General

^1H, ^{13}C and ^{31}P data were recorded on Bruker DPX-200, Bruker DRX-300 and JEOL JNM-LA400 series of instruments for samples in $CDCl_3$. Signal positions are reported in ppm (δ scale) relative to $SiMe_4$

for ^{1}H, $CDCl_3$ for ^{13}C and H_3PO_4 for ^{31}P spectra. Melting points were recorded on Perfit melting point apparatus and are uncorrected. Cyclopentene, cyclohexene, dec-1-ene, crotyl bromide, geranyl bromide and 3-bromocyclohex-1-ene were distilled before use. Cyclooctene, cycloocta-1,5-diene, 1-methylcyclohexene, and allyl bromide were used as received. The mixtures were purified for their components by either gravity column chromatography over silica gel (100-200 mesh) or radial chromatography using plates coated with silica gel 60 PF_{254} (E-Merck). The components were eluted with mixtures of hexanes and EtOAc. IR spectra were measured on Perkin-Elmer 1320 spectrometer.

Argon was bubbled through all the solutions for 30 min before irradiation. Irradiation was carried out using a Hanovia 450W medium pressure mercury lamp (product no.679A0360, arc length 4.3"). The center of the magnetically stirred reaction solution (15-30 mL in quartz tube of id 2.0 cm) was kept at a distance of 11-12 cm from the center of the light source. Water at 25 °C was circulated through the outer jacket of the lamp-housing (all quartz). The reaction solutions were only slightly warm to the touch after the irradiation.

For the thiono-thiolo isomerization, a 10 mM solution of a thionophosphate in CH_3CN was irradiated for 15-30 min. For reactions in solvents such as *i*-PrOH, THF, and toluene and for the allylic benzylation of olefins in CH_3CN, 20 mM solutions of the thionophosphates were used. The molar ratio of thionophosphate and olefin was 1:2 and the irradiation time was 2 h. Radical displacements

on allyl bromides were carried out using solutions (20 mM in CH_3CN) of the thionophosphate and allyl bromide in equimolar ratio for 1 h.

General procedure for the formation of thionophosphates

To an ice-cold stirred suspension of NaH (50%, 0.058 g, 1.2 mmol) in dry THF (2 mL) was added a solution of an alcohol (1.0 mmol) in THF (2 mL). The resultant mixture was stirred till hydrogen evolution ceased (30-60 min). A solution of diethyl chlorothiophosphate (0.207 g, 1.1 mmol) in THF (2 mL) was added, the reaction mixture was allowed to warm to room temperature, and the stirring was continued until the reaction was complete (3-10 h) to TLC. The reaction mixture was diluted with Et_2O (10 mL), mixed with saturated aq NH_4Cl (5 mL) and stirred for 10 min. The layers were separated and the aq layer was extracted with Et_2O (2 x 5mL). The combined Et_2O solution was dried, filtered and concentrated. The residue was chromatographed over silica gel (EtOAc/hexanes) to isolate the desired thionophosphate.

Reaction of methyl mandelate-derived thionophosphate 36a with benzyl bromide and hexabutylditin

A solution of hexabutylditin (0.015 g, 0.025 mmol) in toluene (3.5 mL) was alowly added to a refluxing solution of the thionophosphate **36a** (0.318 g, 1.0 mmol) and benzyl bromide (0.009 g, 0.05 mmol) in toluene (9 mL) over a period of 2 h using a syringe pump. Reflux was continued for an additional 1 h. The solvent was removed and the residue was chromatographed to isolate the starting thionophosphate quantitatively.

Reaction of methyl mandelate-derived thionophosphate 36a with benzyl bromide, tributyltin hydride and AIBN

A solution of Bu_3SnH (0.349 g, 1.2 mmol) and AIBN (0.01 g, 0.06 mmol) in benzene (3.5 mL) was added to a refluxing solution of the thionophosphate **36a** (0.318 g, 1.0 mmol) and benzyl bromide (0.171 g, 1.0 mmol) in benzene (9 mL) over a period of 2 h using a syringe pump. The reaction mixture was refluxed for an additional 1 h before the solvent was removed.

Reaction of methyl mandelate-derived thionophosphate 36a with tributyltin hydride and AIBN

A solution of Bu_3SnH (0.349 g, 1.2 mmol) and AIBN (0.01 g, 0.06 mmol) in benzene (3.5 mL) was added to a refluxing solution of the thionophosphate **36a** (0.318 g, 1.0 mmol) over a period of 2 h using a syringe pump. Refluxing was continued for an additional 1 h before the solvent was removed.

Methyl mandelate-derived thionophosphate 36a. liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60-7.25 (5H, m), 5.89 (1H, d, J = 11.6 Hz), 4.30-4.10 (2H, m), 4.05-3.80 (2H, m), 3.72 (3H, s), 1.35 (3H, t, J = 7.0 Hz), 1.14 (3H, t, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7 (d, J = 6.4 Hz), 135.4 (d, J = 6.0 Hz), 129.7, 129.1, 127.8, 77.9 (d, J = 3.2 Hz), 65.1 (d, J = 5.6 Hz), 64.8 (d, J = 5.8 Hz), 53.0, 16.1 (t, J = 8.3 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 67.2.

Methyl mandelate-derived thiolophosphate 37a. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.30 (5H, m), 5.04 (1H, d, J = 11.3 Hz), 4.20-4.10 (1H, m), 4.08-3.90 (3H, m), 3.74 (3H, s), 1.27 (3H, t, J = 7.0

Hz), 1.24 (3H, t, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8 (d, J = 6.4 Hz), 136.6 (d, J = 6.0 Hz), 129.3, 129.0, 128.7, 64.3 (d, J = 6.2 Hz), 62.2 (d, J = 6.9 Hz), 53.5, 52.3 (d, J = 3.2 Hz), 16.2 (d, J = 7.3 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 23.4.

Dimethyl 2,3-diphenylsuccinate 38 (more polar, solid, mp 231-234 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-6.97 (5H, m), 4.25 (1H, s), 3.69 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 135.6, 128.5, 128.4, 128.3, 127.5, 54.7, 52.4. Calc. *m/z* for [M-MeOH$^+$], 266.0943. Observed *m/z:* 266.0918.

Dimethyl 2,3-diphenylsuccinate 38 (less polar, solid, mp 235-238 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.24 (5H, m), 4.38 (1H, s), 3.39 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 136.3, 128.7, 128.3, 127.9, 54.9, 52.0 Calc. *m/z* for [M-MeOH]$^+$: 266.0943. Observed *m/z:* 266.0923.

Cinnamyl thionophosphate 36b. liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41-7.22 (5H, m), 6.68 (1H, d, J = 15.8 Hz), 6.29 (1H, td, J = 15.8, 6.3 Hz), 4.72 (2H, dd, J = 10.1, 6.3 Hz), 4.22-4.07 (4H, dq, J = 7.1, 9.6 Hz), 1.33 (6H, t, J = 7.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.1, 133.9, 128.6, 128.1, 126.6, 123.6 (d, J = 7.6 Hz), 68.4 (d, J = 4.7 Hz), 64.3 (d, J = 5.5 Hz), 15.9 (d, J = 7.5 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 68.0.

Cinnamyl thiolophosphate 37bi. liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44-7.20 (5H, m), 6.60 (1H, d, J = 15.7 Hz), 6.33-6.18 (1H, td, J = 15.7, 7.4 Hz), 4.30-4.03 (4H, m), 3.65 (2H, dd, J = 14.9, 7.4 Hz), 1.34 (6H, t, J = 7.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.2, 133.4, 128.5,

127.8, 126.3, 124.7 (d, J = 4.7 Hz), 63.5 (d, J = 5.8 Hz), 33.4 (d, J = 4.2 Hz), 15.9 (d, J = 7.2 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 27.3.

1-Phenylallyl thiolophosphate 37bii. liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36-7.25 (5H, m), 6.26-6.08 (1H, m), 5.30-5.16 (2H, m), 4.99 (1H, dd, J = 11.1, 7.8 Hz), 4.22-3.84 (4H, m), 1.25 (6H, t, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.4 (d, J = 5.3 Hz), 137.8 (d, J = 6.2 Hz), 128.6, 127.8, 127.6, 126.3, 116.7, 63.4 (d, J = 4.0 Hz), 52.8, 15.8 (d, J = 7.5 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 25.5.

1-Phenylethyl thionophosphate 36c. liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.23 (5H, m), 5.65-5.50 (1H, m), 4.20-4.00 (2H, m), 4.00-3.80 (2H, m), 1.62 (3H, d, J = 6.6 Hz), 1.30 (3H, t, J = 7.2 Hz), 1.14 (3H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.7, 141.6, 128.4, 128.0, 126.1, 77.4, 64.08, 64.02, 63.96, 23.90, 23.8, 15.8, 15.73, 15.69, 15.58. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 66.8.

1-Phenylethyl thiolophosphate 37c. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.25 (5H, m), 4.48 (1H, dq, J = 10.8, 7.1 Hz), 4.17-3.88 (4H, m), 1.75 (3H, dd, J = 7.1, 1.0 Hz), 1.24 (3H, dt, J = 7.1, 0.7 Hz), 1.23 (3H, dt, J = 7.1, 0.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5 (d, J = 4.9 Hz), 128.6, 127.5, 127.0, 63.8 (d, J = 5.7 Hz), 45.8 (d, J = 4.1 Hz), 24.6 (d, J = 7.5 Hz), 15.9 (d, J = 6.6 Hz). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 26.4.

1,2-Diphenylethyl thionophosphate 36d. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.10 (10H, m), 5.62 (1H, dt, J = 11.7, 6.4 Hz), 3.94-3.84 (2H, m), 3.82-3.74 (1H, m), 3.72-3.56 (1H, m), 3.27 (1H, dd, J =

13.7, 7.7 Hz), 3.08 (1H, ddd, J = 13.7, 6.2, 1.9 Hz), 1.13 (3H, dt, J = 7.1, 0.7 Hz), 1.00 (3H, dt, J = 7.1, 1.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8 (d, J = 2.5 Hz), 136.5, 129.6, 128.1, 128.0, 126.7, 126.4, 81.7 (d, J = 5.8 Hz), 63.7 (d, J = 5.8 Hz), 63.6 (d, J = 5.0 Hz), 44.3 (d, J = 8.2 Hz), 15.6 (d, J = 8.2 Hz), 15.4 (d, J = 8.2 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 66.9.

1,2-Diphenylethyl thiolophosphate 37d. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.08 (10H, m), 4.44 (1H, td, J = 11.7, 7.8 Hz), 4.00-3.85 (2H, m), 3.77-3.63 (2H, m), 3.33-3.28 (1H, dd, J = 13.7, 7.6 Hz), 3.25-3.19 (1H, ddd, J = 13.7, 7.6, 1.4 Hz), 1.16 (3H, dt, J = 7.1, 0.5 Hz), 1.13 (3H, dt, J = 7.1, 0.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 138.1, 129.4, 128.4, 128.2, 127.7, 127.5, 126.6, 63.2 (d, J = 5.7 Hz), 52.6 (d, J = 3.3 Hz), 44.7 (d, J = 8.2 Hz), 15.84 (d, J = 7.4 Hz), 15.75 (d, J = 9.9 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 25.8.

1-Phenylcitronellol (diastereomeric mixture). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35- 7.23 (5H, m), 5.11-5.02 (1H, 2t, J = 7.1 Hz), 4.76-4.70 (1H, 2t, J = 4.5, 6.4 Hz), 2.05-1.85 (3H, m), 1.68-1.57 (6H, 4s), 1.52-1.30 (2H, m), 1.26-1.10 (1H, m), 0.96-0.93 (3H, 2d, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 145.0, 131.2, 131.1, 128.40, 128.39, 127.5, 127.3, 126.0, 125.7, 124.71, 124.68, 72.8, 72.3, 46.7, 46.3, 37.5, 36.8, 29.3, 29.1, 25.6, 25.4, 25.2, 20.1, 19.2, 17.6 Anal. Calcd for $C_{16}H_{24}O$: C, 82.69; H, 10.42. Found: C, 82.50; H, 10.30.

1-Phenylcitronellyl thionophosphate 36e (diastereomeric mixture). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (5H, m), 5.54-5.43

(1H, m), 5.10-5.02 (1H, m), 4.15-3.93 (2H, m), 3.85-3.65 (2H, m), 2.09-1.73 (2H, m), 1.70-1.56 (6H, 4s), 1.26 (6H, dt, J = 7.1, 1.0 Hz), 1.50-1.00 (5H, m), 0.98-0.93 (3H, 2d, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 140.6, 131.3, 131.2, 128.4, 128.3, 128.1, 128.0, 126.9, 126.7, 124.6, 80.1, 80.0, 79.8, 79.7, 64.0, 63.93, 63.88, 45.6, 45.5, 44.93, 44.86, 37.2, 36.7, 28.8, 28.7, 25.7, 25.3, 25.2, 19.7, 19.3, 17.6, 15.83, 15.75, 15.6, 15.5. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 66.6, 66.5.

1-Phenylcitronellyl thiolophosphate 37e (diastereomeric mixture). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.21 (5H, m), 5.10-4.90 (1H, m), 4.38-4.30 (1H, m), 4.10-3.98 (1H, m), 3.98-3.82 (2H, m), 3.82-3.72 (1H, m), 2.10-1.70 (2H, m), 1.68-1.54 (6H, 4s), 1.45-1.14 (11H, m), 0.90 (3H, d, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 142.3, 131.4, 131.3, 128.50, 128.47, 128.4, 127.6, 127.5, 127.4, 127.3, 124.5, 124.4, 63.24, 63.18, 49.12, 49.09, 48.80, 48.77, 45.54, 45.45, 45.0, 44.9, 37.1, 36.2, 30.9, 25.6, 25.2, 19.5, 18.9, 17.6, 15.90, 15.87, 15.82, 15.79. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 25.8, 25.6.

1-Phenyl-5-hexenyl thionophosphate 36f. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (5H, m), 5.80-5.70 (1H, m), 5.44-5.38 (1H, m), 5.01-4.92 (2H, m), 4.16-4.06 (1H, m), 4.06-3.98 (1H, m), 3.89-3.79 (1H, m), 3.79-3.70 (1H, m), 2.10- 2.04 (2H, q, J = 7.1 Hz), 2.05-1.95 (1H, m), 1.85-1.77 (1H, m), 1.53-1.43 (1H, m), 1.43-1.33 (1H, m), 1.27 (3H, t, J = 7.1 Hz), 1.06 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5 (d, J = 3.3 Hz), 138.2, 128.3, 128.0, 126.6,

114.8, 81.2 (d, J = 5.8 Hz), 64.00 (d, J = 4.2 Hz), 63.98, 63.95 (d, J = 4.2 Hz), 37.1 (d, J = 7.4 Hz), 33.2, 24.4, 15.8 (d, J = 8.3 Hz), 15.5 (d, J = 7.4 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 67.2.

1-Phenyl-5-hexenyl thiolophosphate 37f. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.24 (5H, m), 5.78-5.68 (1H, m), 5.00-4.92 (2H, m), 4.27-4.20 (1H, m), 4.10-4.00 (1H, m), 3.99-3.87 and 3.86-3.76 (3H, m), 2.08-1.90 (4H, m), 1.52-1.41 (1H, m), 1.37-1.26 (1H, m), 1.21-1.17 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5, 138.0, 128.5, 127.5, 115.0, 63.3, 50.8, 37.6, 37.5, 33.1, 26.8, 15.9, 15.84, 15.80, 15.76. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 26.3.

Benzyl thionophosphate 36g. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40- 7.25 (5H, m), 5.08 (2H, d, J = 10.0 Hz), 4.15-4.02 (4H, m), 1.3 (3H, t, J = 7.2Hz), 1.26 (3H, t, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8 (d, J = 7.4 Hz), 128.3, 128.2, 127.8, 69.3 (d, J = 4.9 Hz), 64.1 (d, J = 5.8 Hz), 15.7 (d, J = 7.4 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 68.0.

Benzyl thiolophosphate 37g. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.25 (5H, m), 4.03 (2H, d, J = 14.2 Hz), 4.17-4.07 (2H, m), 4.07-3.97 (2H, m), 1.30 (3H, t, J = 7.1Hz), 1.27 (3H, t, J = 7.1Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 128.9, 128.6, 127.6, 63.5 (d, J = 5.8 Hz), 35.0 (d, J = 3.3 Hz), 15.9 (d, J = 7.4 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 26.8.

***trans*-4-(*tert*-Butyl)cyclohexyl thionophosphate 36h.** liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33-4.22 (1H, m), 4.11-4.02 (4H, m), 2.07 (2H,

br d, J = 9.0 Hz), 1.76 (2H, br d, J = 12.0 Hz), 1.45-1.30 (2H, m), 1.29 (6H, t, J = 7.0 Hz), 1.10- 0.85 (3H, m), 0.86 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 79.0, 78.9, 63.92, 63.86, 46.7, 33.61, 33.57, 33.2, 27.5, 25.4, 15.9, 15.8. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 66.4.

1-Methyl-2-phenethyl thionophosphate 36i. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.20 (5H, m), 4.85-4.77 (1H, m), 4.12-3.82 (4H, m), 3.05-3.00 (1H, dd, J = 13.7, 6.6 Hz), 2.84-2.78 (1H, dd, J = 13.7, 6.6 Hz), 1.30 (3H, d, J = 6.1 Hz), 1.29 (3H, dt, J = 7.1, 0.8 Hz), 1.22 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 129.6, 128.3, 126.5, 77.1 (d, J = 5.8 Hz), 63.9 (t, J = 5.0 Hz), 43.6 (d, J = 6.6 Hz), 20.9 (d, J = 3.3 Hz), 15.9 (d, J = 4.1 Hz), 15.8 (d, J = 5.0 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 66.5.

(*E*)-2-Butenyl thionophosphate 36j. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85-5.77 (1H, m), 5.65-5.58 (1H, m), 4.51-4.46 (2H, m), 4.18-4.06 (4H, m), 1.74-1.72 (3H, dd, J = 6.4, 1.2 Hz), 1.40-1.26 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.4, 125.6, 77.4, 68.6, 64.2, 17.7, 15.8. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 67.8.

Methyl 3-hydroxy-3-methyl-2-phenylbutanoate 42. liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.26 (5H, m), 3.68 (3H, s), 3.60 (1H, s), 1.34 (3H, s), 1.07 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 135.3, 129.5, 128.3, 127.6, 71.7, 60.4, 52.0, 29.5, 26.6. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.19; H, 7.75. Found: C, 68.98; H, 7.81.

Methyl α-phenyl-α-(2-tetrahydrofuranyl)acetate 43. liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33-7.26 (5H, m), 4.58-4.46 (1H, m),

3.98-3.77 (2H, m), 3.70 (3H, s), 3.51 (1H, d, J = 9.9 Hz), 1.92-1.74 (2H, m), 1.74- 1.61 (1H, m), 1.51-1.34 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 135.9, 128.7, 128.4, 127.7, 80.6, 68.5, 57.5, 52.1, 29.5, 25.4. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.87; H, 7.33. Found: C, 70.65; H, 7.18.

Methyl 2,3-diphenylpropanoate 44. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.10 (10H, m), 3.88-3.82 (1H, dd, J = 8.7, 6.9 Hz), 3.6 (3H, s), 3.45- 3.38 (1H, dd, J = 13.5, 8.7 Hz), 3.06-2.99 (1H, dd, J = 13.5, 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 139.0, 138.6, 128.9, 128.6, 128.3, 127.9, 127.4, 126.4, 53.6, 52.0, 39.8. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.96; H, 6.72. Found: C, 79.80; H, 6.84.

2-Methyl-5-phenyl-4-penten-2-ol 45 (1:1 mixture of *cis*- and *trans*-isomers). liquid. Characteristic ^{1}H signals for the *E*-derivative (400 MHz, $CDCl_3$): δ 6.46 (1H, d, J = 15.9 Hz), 6.32-6.25 (1H, td, J = 15.9, 7.3 Hz), 2.52 (2H, dd, J = 7.5, 1.7 Hz). Characteristic ^{1}H signals for the *Z*-derivative (400 MHz, $CDCl_3$): δ 6.60 (1H, d, J = 11.7 Hz), 5.84-5.78 (1H, td, J = 11.7, 7.5 Hz), 2.38 (2H, d, J = 7.5 Hz). The methyl groups appear at δ 1.27 in one isomer and at δ 1.25 in the other.

2-[(*E*)-3-Phenyl-2-propenyl]tetrahydrofuran 47a. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.17 (5H, m), 6.46 (1H, d, J = 15.6 Hz), 6.28-6.20 (1H, td, J = 15.6, 7.1 Hz), 3.98-3.88 (2H, m), 3.78-3.72 (1H, m), 2.53-2.38 (2H, m), 2.10-1.75 (4H, m). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.77; H, 8.45.

2-[(*Z*)-3-Phenyl-2-propenyl]tetrahydrofuran 47b. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (5H, m), 6.53 (1H, d, J = 11.7 Hz),

5.76-5.70 (1H, td, J = 11.7, 7.1 Hz), 3.98-3.84 (2H, m), 3.77-3.70 (1H, m), 2.68-2.60 (1H, m), 2.56-2.49 (1H, m), 2.03-1.95 (1H, m), 1.92-1.83 (2H, m), 1.55-1.46 (1H, m). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.80; H, 8.42.

Methyl α-(2-cyclopentenyl)-α-phenylacetate 60. Diastereomeric mixture, liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43-7.18 (5H, m), 5.87-5.68 and 5.32-5.26 (2H, m), 3.65 (3H, s), 3.55-3.24 (2H, m), 2.45-2.10 (2H, m), 1.83-1.17 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.4, 174.3, 139.5, 139.4, 133.9, 133.1, 132.8, 129.4, 129.3, 128.2, 123.0, 58.3, 57.9, 52.1, 52.0, 50.4, 50.1, 32.5, 32.1, 29.6, 28.3. ν_{max} (film) 2920, 1718, 1440, 1420, 1160 cm^{-1}. Calc. M^+ for $C_{14}H_{16}O_2$: 216.1149. Observed M^+: 216.1157. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.62; H, 7.35.

Methyl α-(2-cyclohexenyl)-α-phenylacetate 61. Diastereomeric mixture; liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.18 (5H, m), 5.85-5.75, 5.70-5.60 and 5.20-5.10 (2H, m), 3.66 and 3.65 (3H, s), 3.32 (1H, d, J = 11.1 Hz), 2.95-2.75 (1H, m), 2.03-1.25 and 1.10-0.95 (6H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.0, 173.9, 137.7, 137.4, 129.2, 129.0, 128.8, 128.5, 128.4, 127.9, 127.3, 57.5, 51.8, 38.5, 38.4, 27.9, 26.4, 25.3, 25.2, 21.1, 20.7. ν_{max} (film) 2920, 1720, 1442, 1425, 1150 cm^{-1}. Calc. M^+ for $C_{15}H_{18}O_2$: 230.1306. Observed M^+: 230.1300. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 78.11; H, 7.73.

Methyl α-(2-cyclooctenyl)-α-phenylacetate 62. Diastereomeric mixture, low-melting solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.18

(5H, m), 5.83-5.71, 5.57-5.46, 5.36-5.27 and 5.02-4.93 (2H, m), 3.65 and 3.62 (3H, s), 3.46 and 3.42 (1H, d, J = 7.2 Hz) 3.45-3.16 (1H, m), 2.42-1.93 (2H, m), 1.77-1.17 and 1.03- 0.85 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 174.0, 138.0, 137.7, 131.6, 131.3, 130.4, 128.6, 128.4, 127.3, 127.2, 57.9, 57.7, 51.9, 51.8, 39.5, 38.8, 34.7, 33.0, 29.5, 26.9, 26.8, 25.6, 25.3. Calc. $M^+$for $C_{17}H_{22}O_2$: 258.1618. Observed M^+: 258.1610. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.02; H, 8.59. Found: C, 78.88; H, 8.45.

Methyl α-(1-methyl-2-cyclohexenyl)-α-phenylacetate 64b. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.26 (5H, m), 5.70-5.56 (2H, m), 3.64 (3H, s), 3.54 (1H, s), 1.94-1.25 (6H, m), 1.09 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 133.4, 130.2, 130.1, 127.8, 127.7, 127.1, 127.0, 60.9, 59.9, 51.5, 51.4, 38.3, 37.9, 33.4, 33.1, 25.1, 24.9, 24.8, 24.5, 18.9, 18.7. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.64; H, 8.26. Found: C, 78.45; H, 8.16.

Methyl α-(3-methyl-2-cyclohexenyl)-α-phenylacetate 64a and methyl α-(2-methyl-2-cyclohexenyl)-α-phenylacetate 64c (diastereomeric mixture). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.25 (m), 5.49 (br s), 5.40 (br s), 5.33 (br s), 4.87 (br s), 3.78 (d, J = 10.0 Hz), 3.68-3.65 (4s), 3.58 (d, J = 10.0 Hz), 3.30-3.26 (2d, J = 11.0, 11.5 Hz), 2.83 (br s), 2.05-1.70 (m), 1.69, 1.67, 1.58, and 1.53 (4s), 1.50-1.20 (m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 137.8, 137.5, 136.4, 136.1, 128.8, 128.7, 128.5, 128.44, 128.42, 128.35, 128.3, 127.2, 123.0, 121.8, 57.7, 57.6, 52.0, 51.83, 51.76, 38.8, 38.7, 30.0, 27.7, 25.9, 24.0, 23.9, 21.5, 21.0, 18.3.

Methyl 2-phenyl-4-dodecenoate 65a and methyl 2-phenyl-3-vinyldecanoate 65b (diastereomeric mixture). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.23 (m), 5.67-5.58 (m), 5.49-5.39 (m), 5.37-5.21 (m), 5.14-5.07 (m), 4.85-4.74 (m), 3.66-3.59 (4s), 3.46-3.41 (2d, J = 11.0 Hz), 2.84-2.68 (m), 2.50-2.36 (m), 1.95-1.90 (q, J = 6.8 Hz), 1.40-1.0 (m), 0.89-0.82 (2t, J = 7.0 Hz).

3-(2-Cyclohexenyl)-1-phenylpropene 66a (mixture of *E*- and *Z*-isomers). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.19 (m), 6.49-6.46 (d, J = 12.0 Hz), 6.42-6.38 (d, J =15.8 Hz), 6.26-6.19 (td, J = 16.0, 6.8 Hz), 5.74-5.67 (m), 5.64-5.59 (dt, J = 8.3, 1.7 Hz), 2.43-2.28 (m), 2.28-2.18 (m), 2.02-1.98 (m), 1.84-1.75 (m), 1.75-1.65 (m), 1.60-1.45 (m), 1.38-1.22 (m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 137.7, 131.34, 131.27, 131.1, 129.7, 129.3, 128.8, 128.5, 128.1, 127.5, 127.4, 126.8, 126.4, 125.9, 39.8, 35.9, 35.5, 35.0, 28.91, 28.88, 25.27, 25.25, 21.42, 21.39. Anal. Calcd for $C_{15}H_{18}$: C, 90.84; H, 9.16. Found: C, 90.60; H, 9.02.

3-(Cyclohex-2-enyl)-3-phenylpropene 66b (more polar). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.18 (5H, m), 6.03-5.94 (1H, m), 5.65-5.60 (1H, m), 5.33-5.30 (1H, dd, J = 10.2, 2.2 Hz), 5.05-5.00 (2H, m), 3.05 (1H, t, J = 9.3 Hz), 2.51-2.44 (1H, m), 1.99-1.94 (2H, m), 1.87-1.78 (1H, m), 1.76-1.71 (1H, m), 1.56-1.47 (1H, m), 1.37-1.25 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 140.9, 129.7, 128.4, 128.1, 127.9, 126.1, 115.1, 56.4, 39.7, 27.5, 25.3, 21.5. Anal. Calcd for $C_{15}H_{18}$: C, 90.84; H, 9.16. Found: C, 90.68; H, 9.05.

3-(Cyclohex-2-enyl)-3-phenylpropene 66b (less polar). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.17 (5H, m), 6.06-5.97 (1H, m), 5.80-5.72 (2H, m), 5.10-5.04 (2H, m), 3.04 (1H, t, J = 9.3 Hz), 2.47-2.41 (1H, m), 1.99-1.95 (2H, m), 1.71-1.65 (1H, m), 1.51-1.39 (2H, m), 1.17- 1.07 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 140.6, 129.5, 128.4, 128.1, 127.8, 126.1, 115.7, 56.2, 39.6, 27.7, 25.4, 21.6. Anal. Calcd for $C_{15}H_{18}$: C, 90.84; H, 9.16. Found: C, 90.65; H, 9.02.

1-(Cyclohex-2-enyl)-1-phenylethane 67 (diastereomeric mixture). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.16 (10H, m), 5.82-5.79 (1H, m), 5.76-5.71 (1H, m), 5.65-5.60 (1H, m), 5.39-5.35 (1H, m), 2.62-2.53 (2H, m), 2.35-2.18 (2H, m), 2.18-2.00 (4H, m), 1.85-1.40 (8H, m), 1.28 (3H, d, J = 7.0 Hz), 1.24 (3H, d, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.7, 129.6, 128.1, 127.8, 127.5, 125.8, 45.0, 44.7, 41.8, 27.6, 26.5, 25.4, 25.3, 22.0, 21.4, 18.8, 18.5. Anal. Calcd for $C_{14}H_{18}$: C, 90.25; H, 9.75. Found: C, 90.10; H, 9.58.

Methyl α-(2,6-cyclooctadienyl)-α-phenylacetate 63a (diastereomeric mixture) and methyl α-(2,5-cyclooctadienyl)-α-phenylacetate 63b (diastereomeric mixture). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.25 (m), 5.67-5.50 (m), 5.47-5.37 (m), 5.07-5.02 (dd, J = 11.5, 6.8 Hz), 3.66 (s), 3.65 (s), 3.57-3.45 (m), 3.43-3.36 (2d, J = 10.5 Hz), 2.60-2.48 (m), 2.44-2.26 (m), 2.23-2.13 (m), 2.03-1.92 (m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 173.8, 137.5, 137.4, 130.9, 130.3, 129.6, 129.2, 128.91, 128.86, 128.7, 128.6, 128.5, 128.4, 127.6, 127.5, 127.4, 127.3, 58.4, 58.1, 52.0, 51.9, 42.2, 42.1, 33.1,

31.9, 27.9, 27.8, 27.5. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.64; H, 7.87. Found: C, 79.48; 7.69.

3-Benzyl-1,5-cyclooctadiene 68a. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.17 (5H, m), 5.59-5.51 (3H, m), 5.43-5.38 (1H, dd, J = 11.7, 6.3 Hz), 3.05- 2.96 (1H, m), 2.75-2.70 (1H, dd, J = 13.4, 6.8 Hz), 2.60-2.55 (1H, dd, J = 13.4, 7.8 Hz), 2.53-2.44 (1H, m), 2.39-2.25 (3H, m), 2.24-2.13 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 133.6, 129.1, 128.8, 128.2, 128.0, 127.7, 125.9, 43.1, 41.0, 33.7, 28.2, 27.6. Anal. Calcd for $C_{15}H_{18}$: C, 90.84; H, 9.16. Found: C, 90.67; H, 9.04.

6-Benzyl-1,4-cyclooctadiene 68b. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.15 (5H, m), 5.71-5.58 (2H, m), 5.43-5.35 (1H, m), 5.18-5.12 (1H, m), 3.14-3.04 (1H, m), 2.86-2.56 (5H, m) 1.97-1.90 (1H, m), 1.56-1.47 (1H, m), 1.18-1.10 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 133.8, 129.8, 129.0, 128.6, 128.4, 128.1, 125.7, 42.3, 37.1, 29.9, 29.8, 24.5. Anal. Calcd for $C_{15}H_{18}$: C, 90.84; H, 9.16. Found: C, 90.69; H, 9.06.

1-Phenyl-1,5-hexadiene (mixture of *E*- and *Z*-isomers). liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.18 (m), 6.44-6.37 (unsym t), 6.22 (t, J = 6.4 Hz), 6.20 (t, J = 6.8 Hz), 5.92-5.78 (m), 5.67 (t, J = 7.1 Hz), 5.64 (t, J = 7.1 Hz), 5.08-4.96 (m), 2.47-2.40 (dq, J = 7.3, 1.7 Hz), 2.33-2.25 (m), 2.65-2.17 (m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 138.0, 137.7, 137.6, 132.0, 130.2, 130.1, 129.2, 128.7, 128.4, 128.1, 126.9, 126.5, 125.9, 115.0, 114.9, 33.9, 33.5, 32.4, 27.9. Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.87; H, 8.75.

Allyl thiolophsphate 72. colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96-5.86 (1H, m), 5.30-5.26 (1H, dd, J = 16.8, 1.2 Hz), 5.16-5.14 (1H, dd, J = 10.0, 1.0 Hz), 4.25-4.10 (4H, m), 3.50-3.44 (2H, tdd, J = 14.6, 7.1, 1.0 Hz), 1.368 (3H, t, J = 7.1 Hz), 1.366 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.7 (d, J = 5.0 Hz), 118.3, 63.6 (d, J = 5.7 Hz), 33.5 (d, J = 4.1 Hz), 16.0 (d, J = 7.4Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 27.3.

2-Cyclohexenyl thiolophosphate 73. colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84- 5.74 (2H, m), 4.25-4.12 (4H, m), 3.99 (1H, br d, J = 5.8 Hz), 2.15-1.94 (4H, m), 1.85-1.75 (1H, m), 1.73-1.63 (1H, m), 1.37 (6H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.7, 127.5 (d, J = 7.5 Hz), 63.53, 63.47, 63.4, 42.6 (d, J = 3.3 Hz), 31.0 (d, J = 4.1 Hz), 24.6, 19.4, 16.1 (d, J = 7.4 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 27.5.

Geranyl thiolophosphate 74. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (1H, t, J = 8.1 Hz), 5.07 (1H, t, J = 6.8 Hz), 4.25-4.09 (4H, m), 3.51-3.46 (2H, dd, J = 12.6, 7.7 Hz), 2.13-1.96 (4H, m), 1.74-1.60 (9H, m), 1.37 (6H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 131.9, 123.7, 119.2, 63.4, 39.6, 28.8, 26.3, 25.7, 25.5, 17.7, 16.1. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 28.1.

75. colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (1H, s), 5.92 (1H, s), 4.26 (2H, q, J = 7.2 Hz), 4.21-4.07 (4H, m), 3.72 (2H, d, J = 15.2 Hz), 1.35 (6H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 136.9 (d, J = 3.3 Hz), 128.0, 63.5 (d, J =

5.7 Hz), 61.1, 31.4 (d, J = 4.2 Hz), 15.9 (d, J = 7.4 Hz), 14.1. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 27.0.

***trans*-1,4-Diphenyl-3-butenyl thionophosphate 82**. liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.19 (10H, m), 6.43 (1H, d, J = 15.8 Hz), 6.16-6.08 (1H, td, J = 15.8, 7.3 Hz), 5.57-5.51 (1H, m), 4.13-3.72 (1H each, 4m), 2.92-2.84 (1H, m), 2.78-2.71 (1H, m), 1.21 (3H, t, J = 7.1 Hz), 1.06 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0, 137.2, 133.2, 128.43, 128.35, 128.2, 127.2, 126.6, 126.1, 124.8, 80.6 (d, J = 5.8 Hz), 64.1 (d, J = 3.3 Hz), 64.0 (d, J = 3.3 Hz), 41.4 (d, J = 7.4 Hz), 15.7 (d, J = 8.2 Hz), 15.6 (d, J = 7.4 Hz). ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 67.0.

Bis-[(*E*)-1,4-diphenyl-3-butenyl]ether 83. Liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39- 7.20 (20H, m), 6.47 (2H, d, J = 15.9 Hz), 6.10-6.03 (2H, td, J = 15.9, 7.1 Hz), 5.87-5.83 (2H, dd, J = 7.8, 6.3 Hz), 2.92-2.84 (2H, m), 2.78-2.70 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 136.7, 134.2, 129.0, 128.8, 128.5, 127.6, 126.5, 126.2, 123.1, 85.0, 38.1. Anal. Calcd for $C_{32}H_{30}O$: C, 89.25; H, 7.03. Found: C, 89.13; H, 6.91.

The adduct of TEMPO and the radical 52. solid (mp 73- 75 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (2H, d, J = 7.1 Hz), 7.35-7.28 (3H, m), 5.21 (1H, s), 3.65 (3H, s), 1.60-1.20 (6H, m), 1.23 (3H, s), 1.14 (3H, s), 1.07 (3H, s), 0.72 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 138.1, 128.2, 127.8, 126.8, 88.5, 59.8, 51.7, 40.1, 40.0, 33.4, 32.7, 20.1, 17.0.

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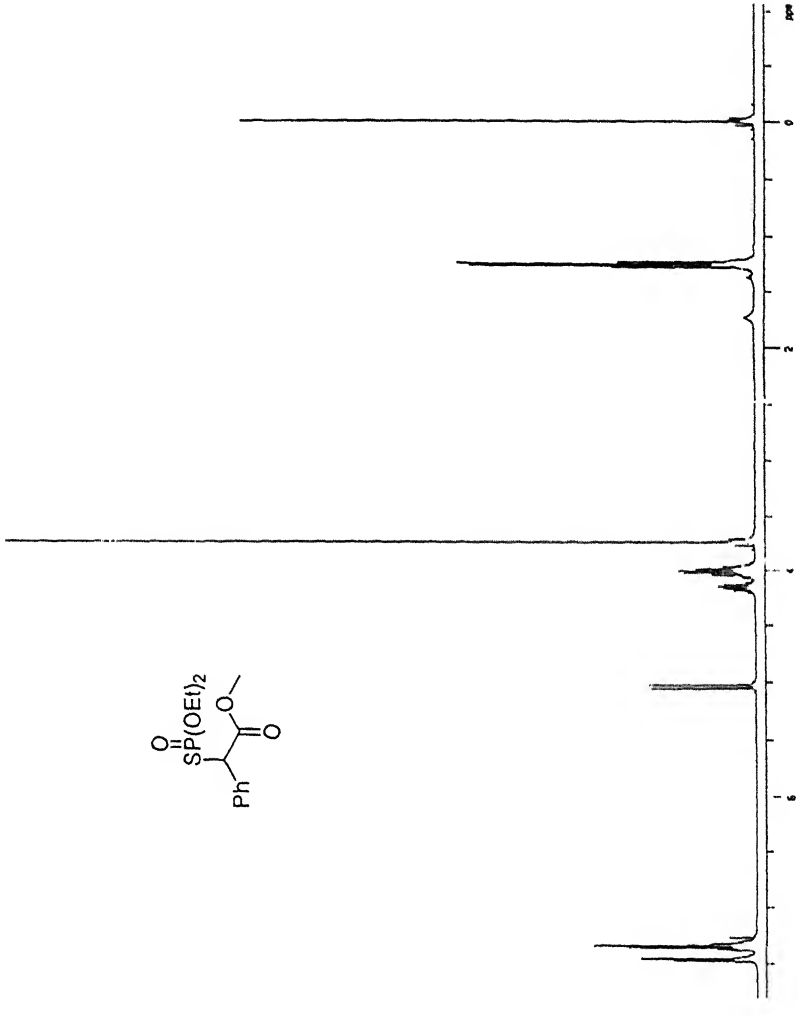


Figure 7. 400 MHz ^{1}H NMR spectrum of **37a**

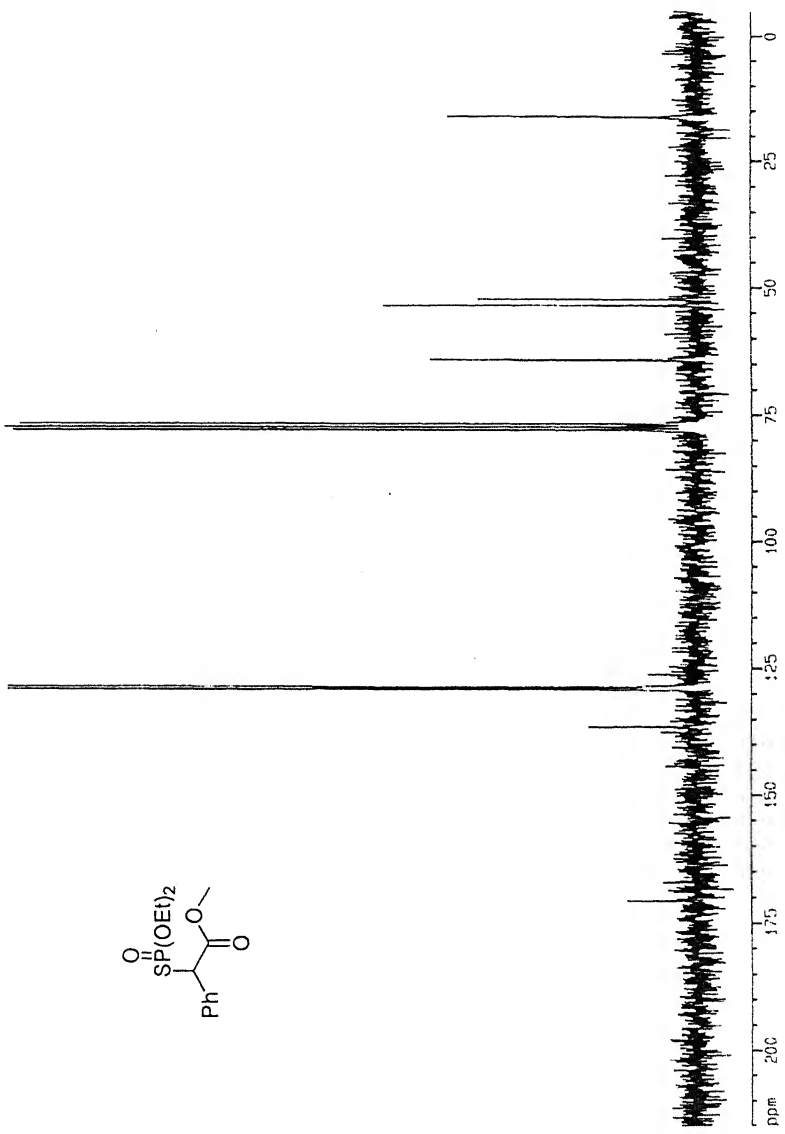


Figure 8. 50 MHz ^{13}C NMR spectrum of **37a**

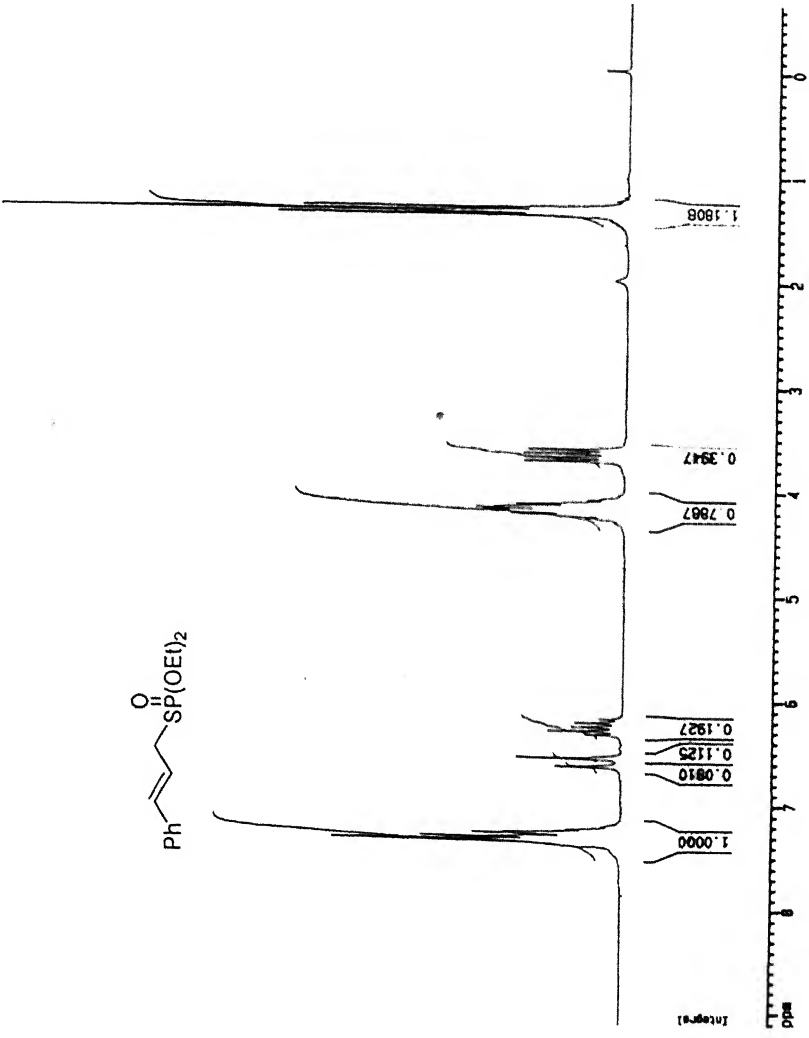


Figure 9. 200 MHz ^{1}H NMR spectrum of **37bi**

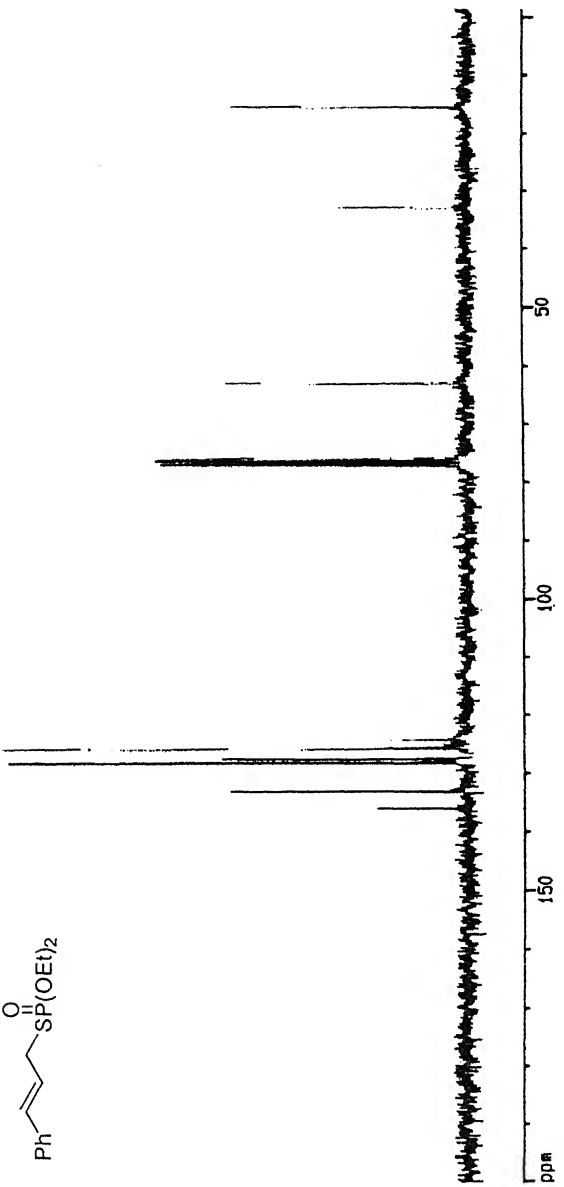


Figure 10. 50 MHz ^{13}C NMR spectrum of **37bi**

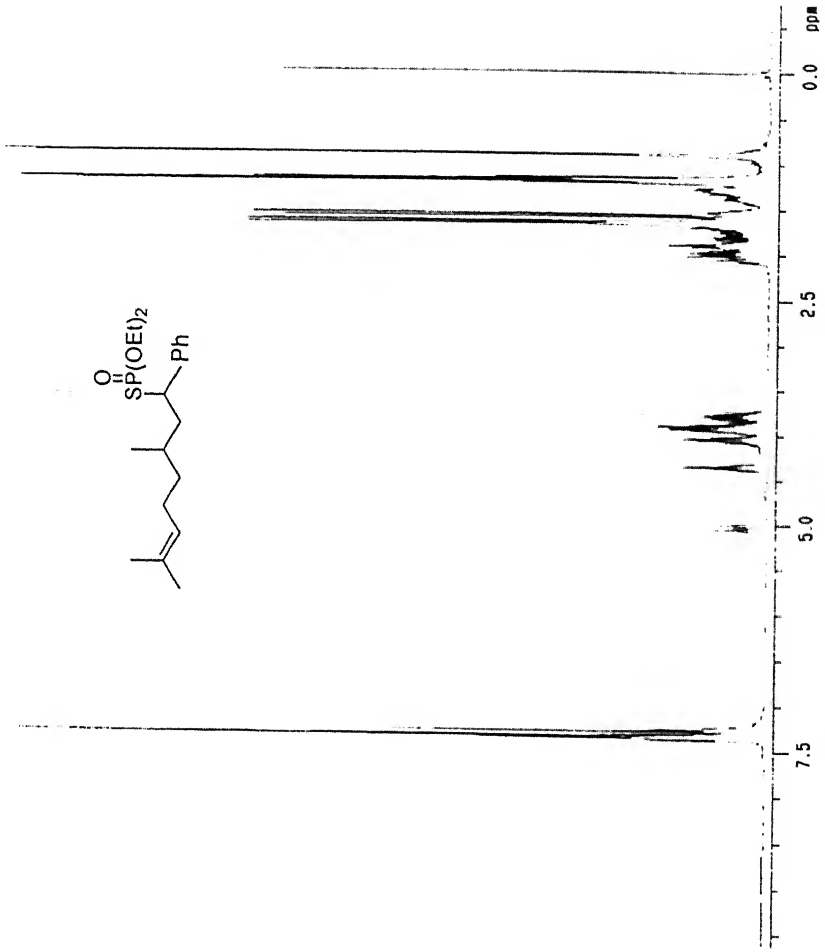


Figure 11. 400 MHz ^{1}H NMR spectrum of **37e**

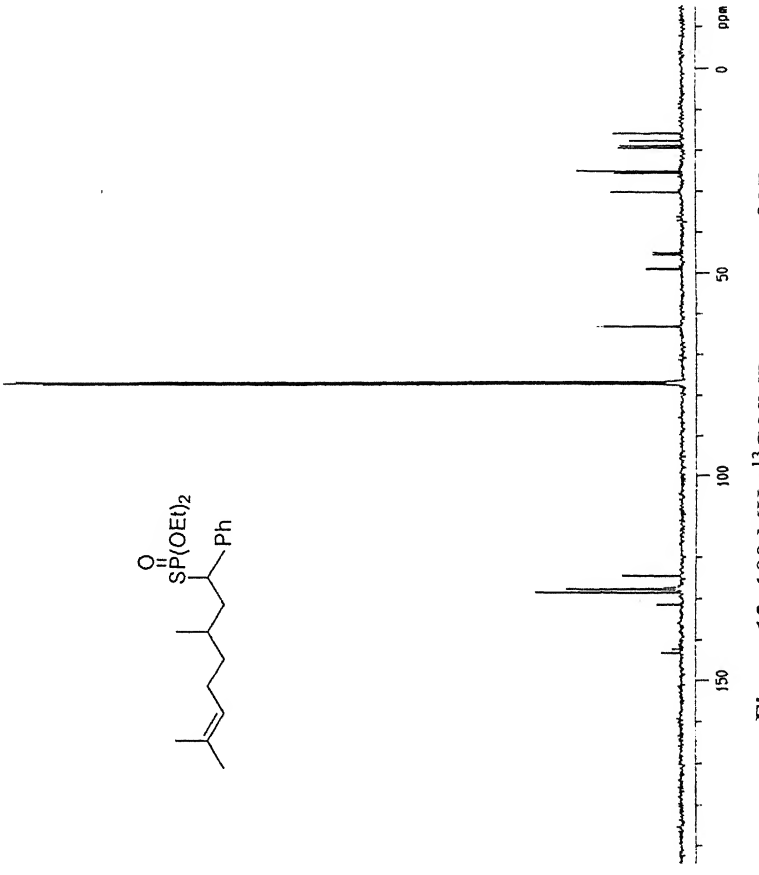


Figure 12. 100 MHz ^{13}C NMR spectrum of **37e**

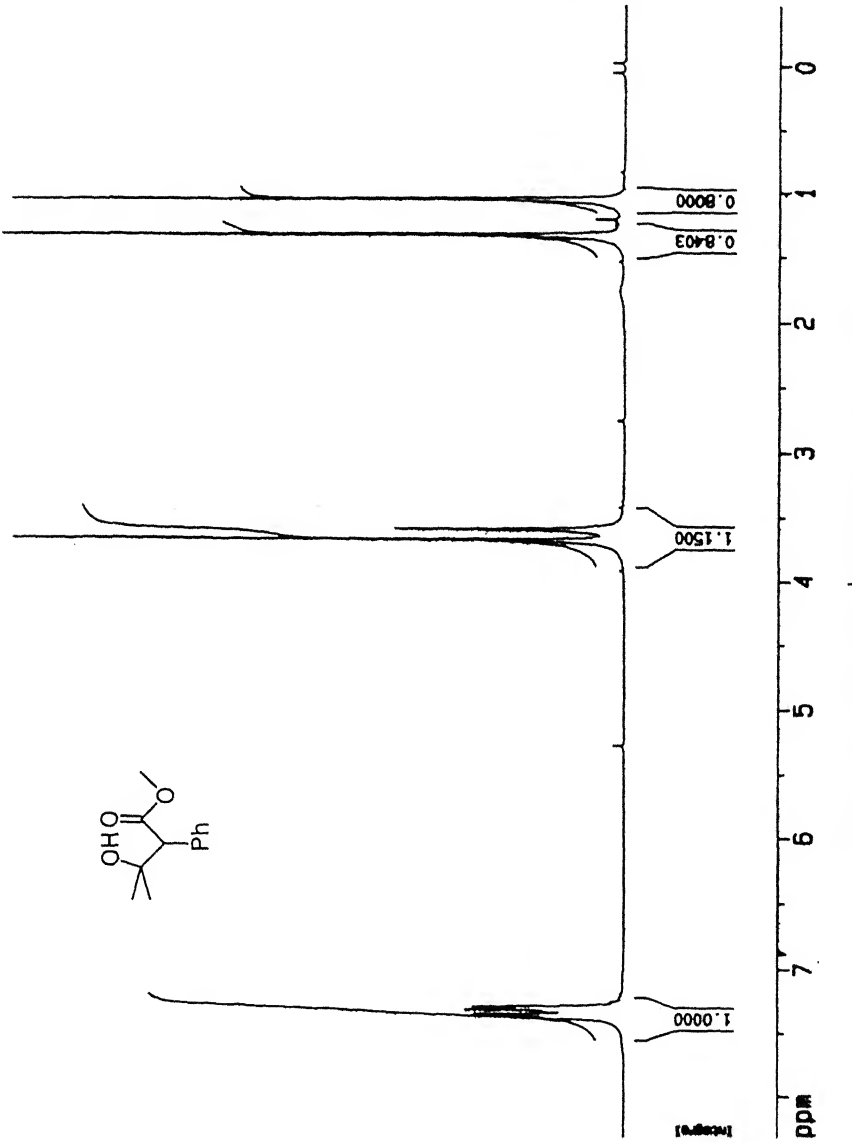


Figure 13. 300 MHz ^{1}H NMR spectrum of **42**

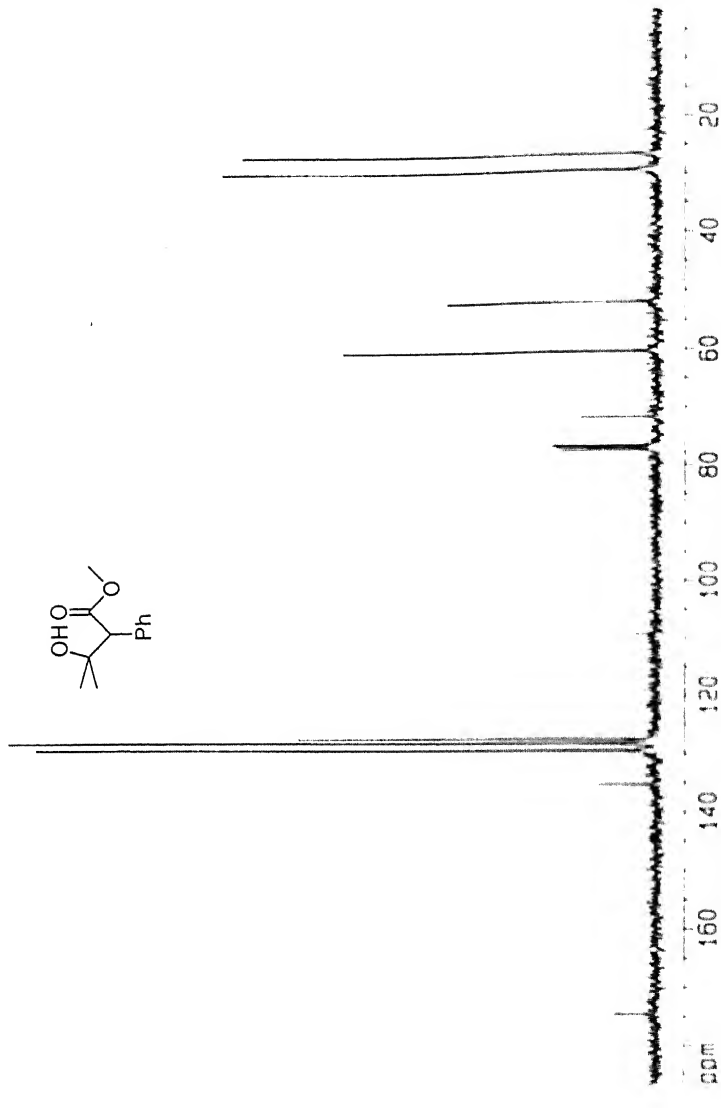


Figure 14. 75 MHz ^{13}C NMR spectrum of **42**

Figure 15. 200 MHz ^{1}H NMR spectrum of **43**

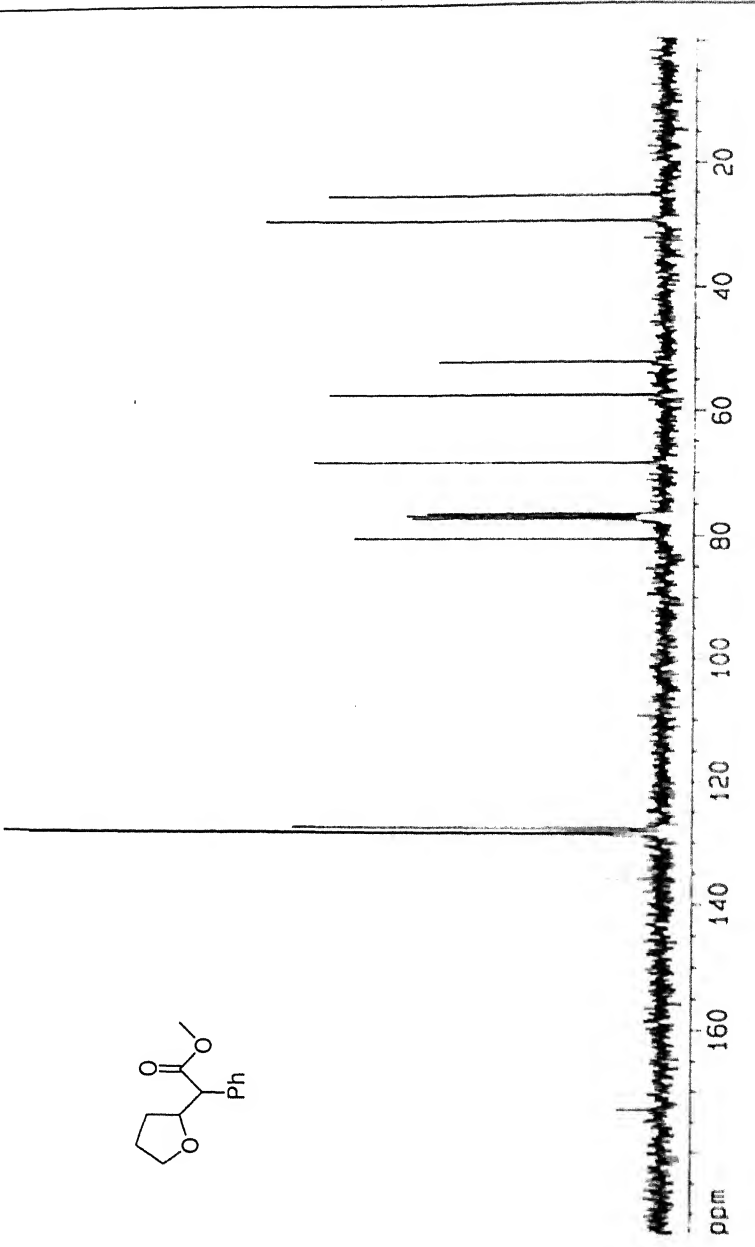


Figure 16. 75 MHz ^{13}C NMR spectrum of **43**

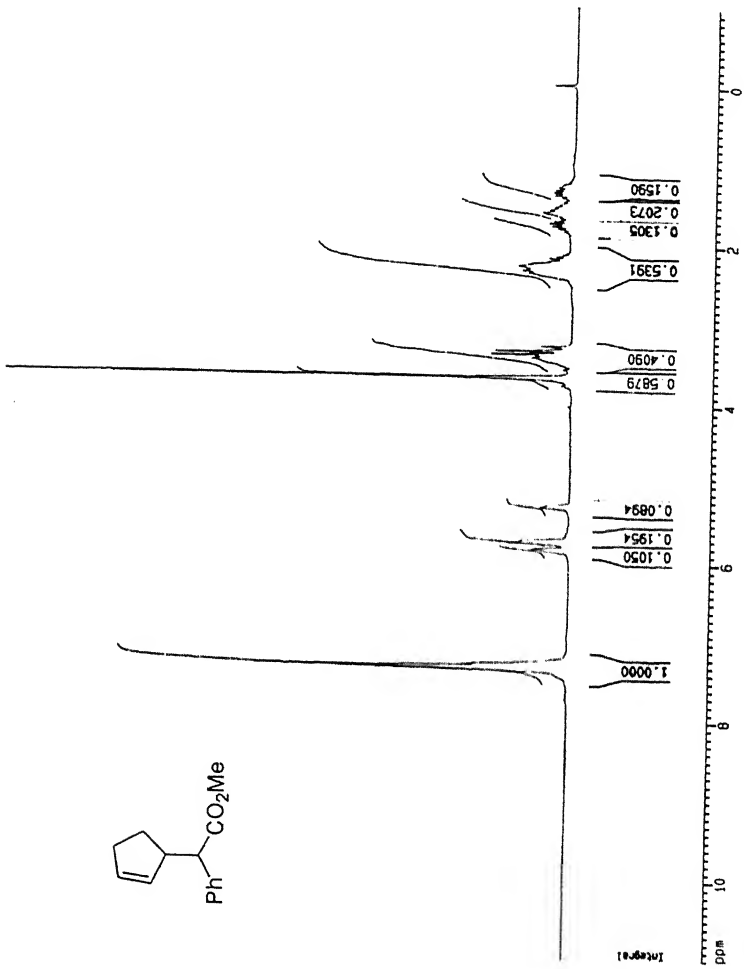


Figure 17. 200 MHz ^{1}H NMR spectrum of **60**

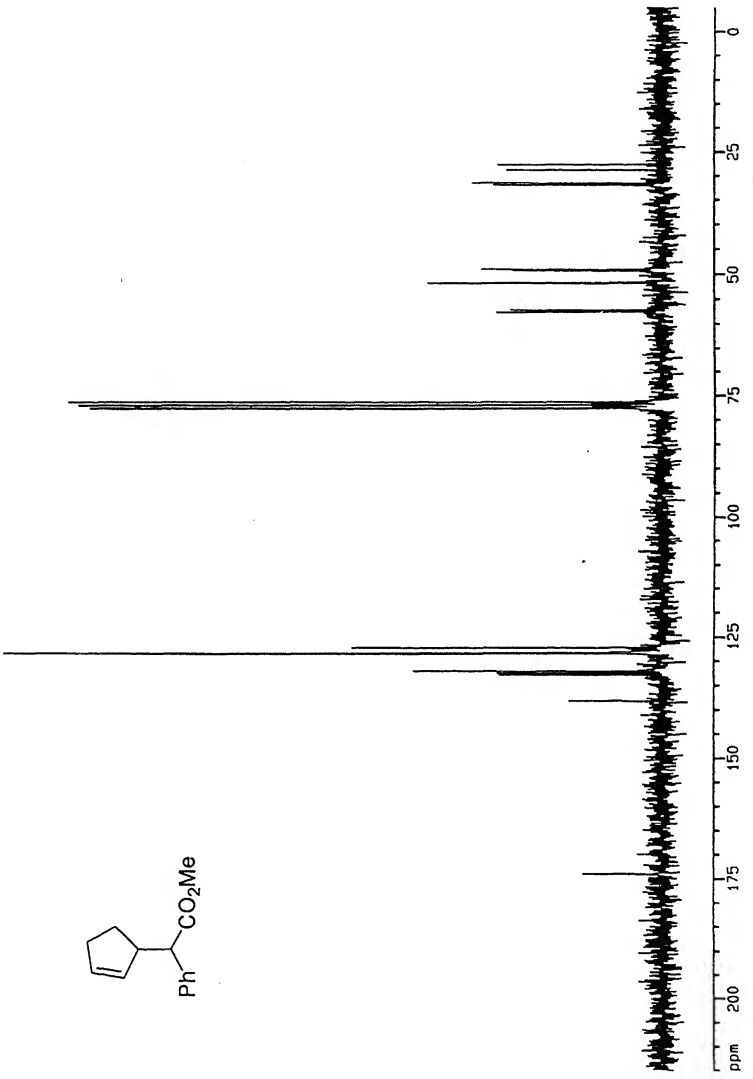


Figure 18. 50 MHz ^{13}C NMR spectrum of **60**

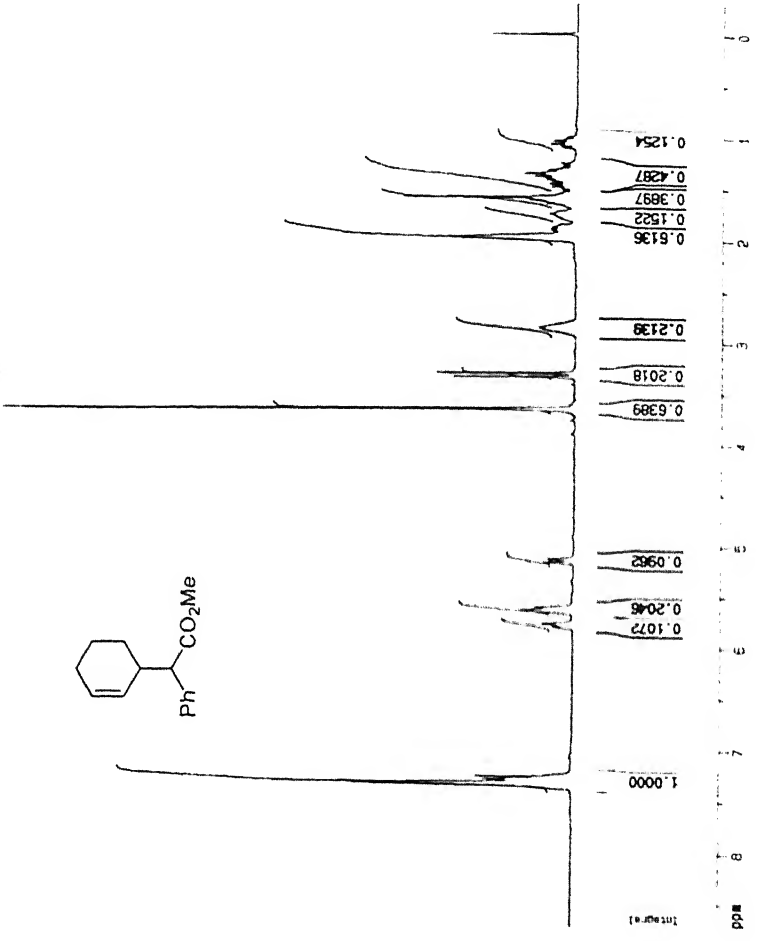


Figure 19. 300 MHz ^{1}H NMR spectrum of **61**

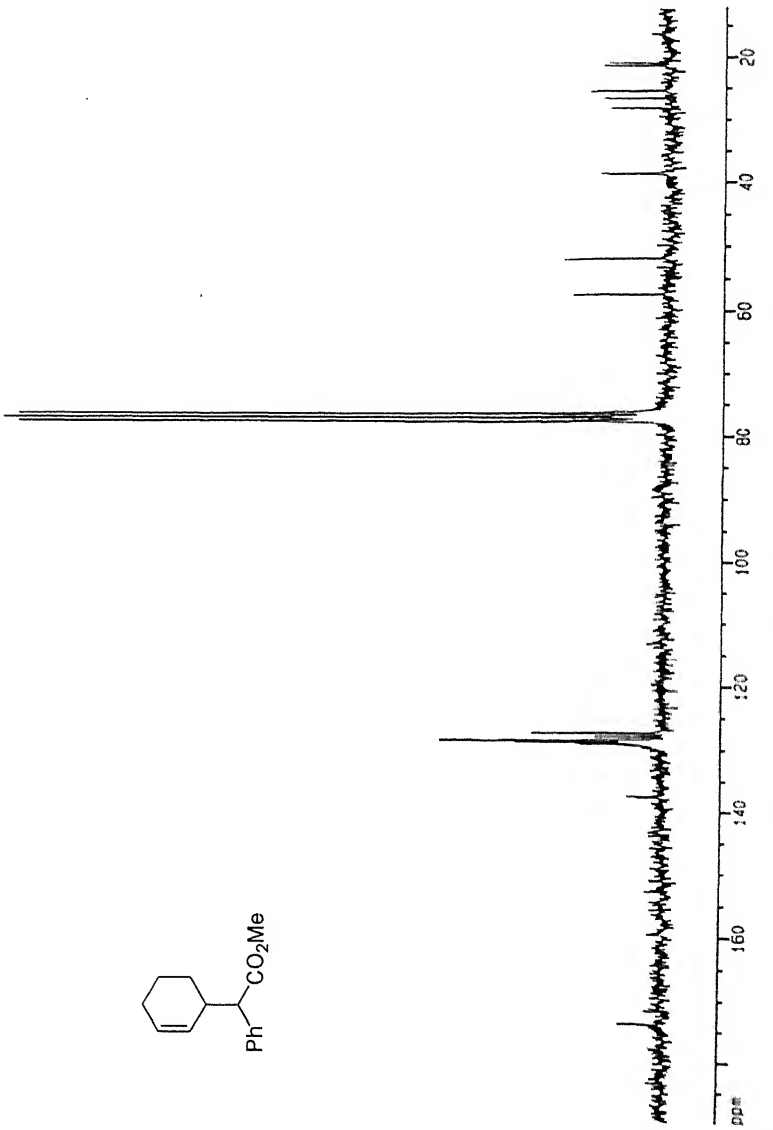


Figure 20. 50 MHz ^{13}C NMR spectrum of **61**

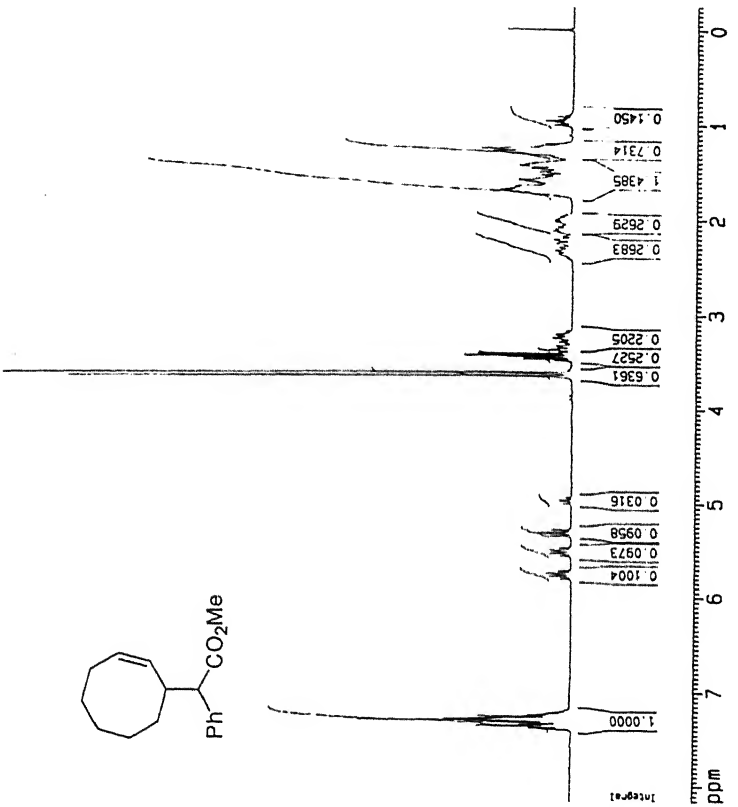


Figure 21. 300 MHz ^{1}H NMR spectrum of **62**

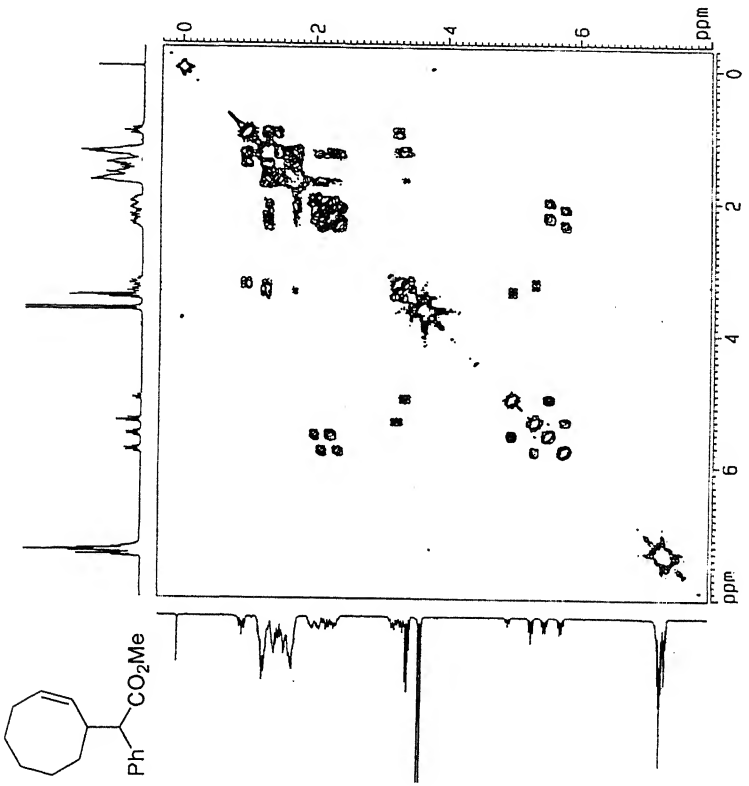


Figure 22. 300 MHz COSY spectrum of **62**

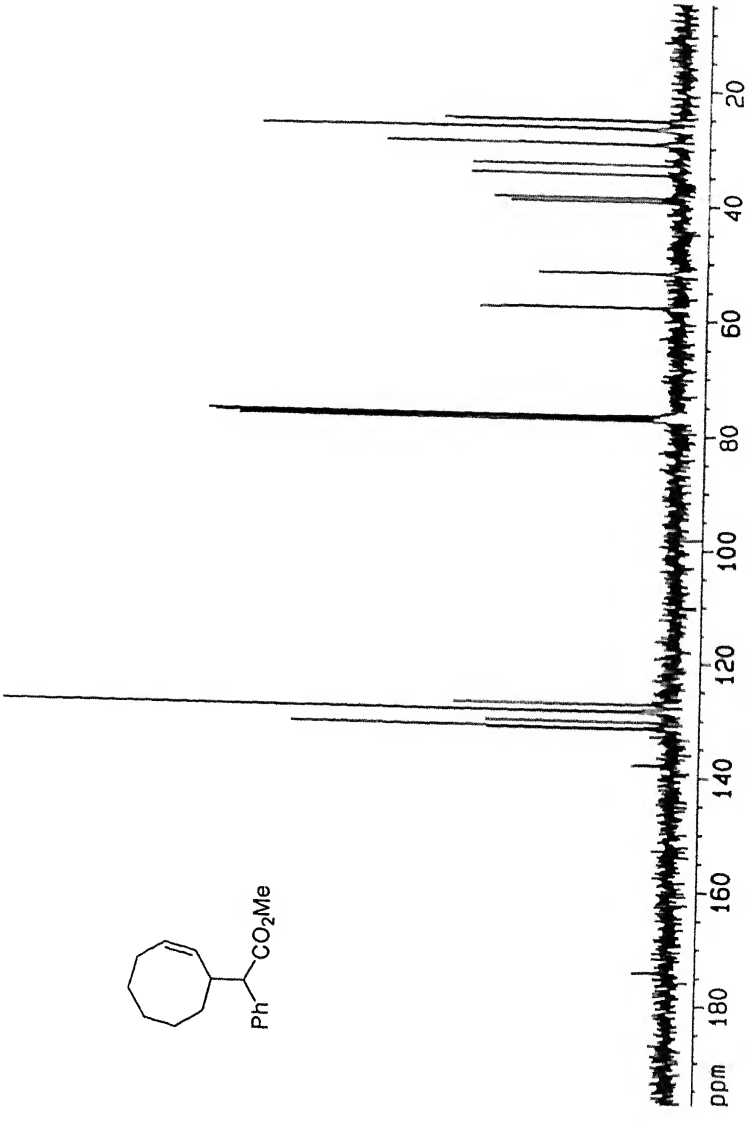


Figure 23. 75 MHz ^{13}C NMR spectrum of **62**

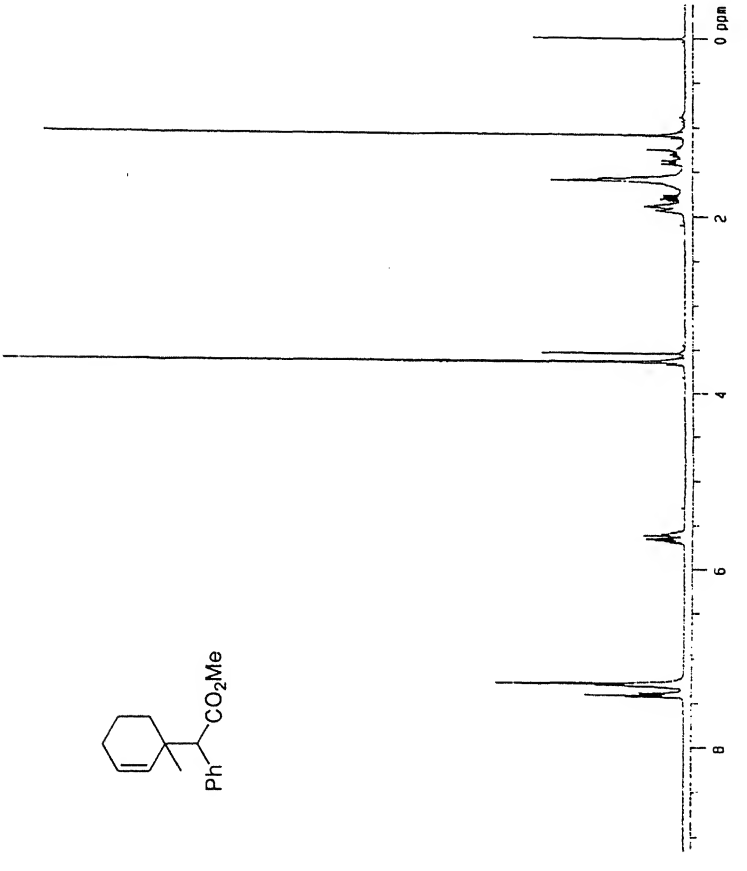


Figure 24. 400 MHz ^{1}H NMR spectrum of **64b**

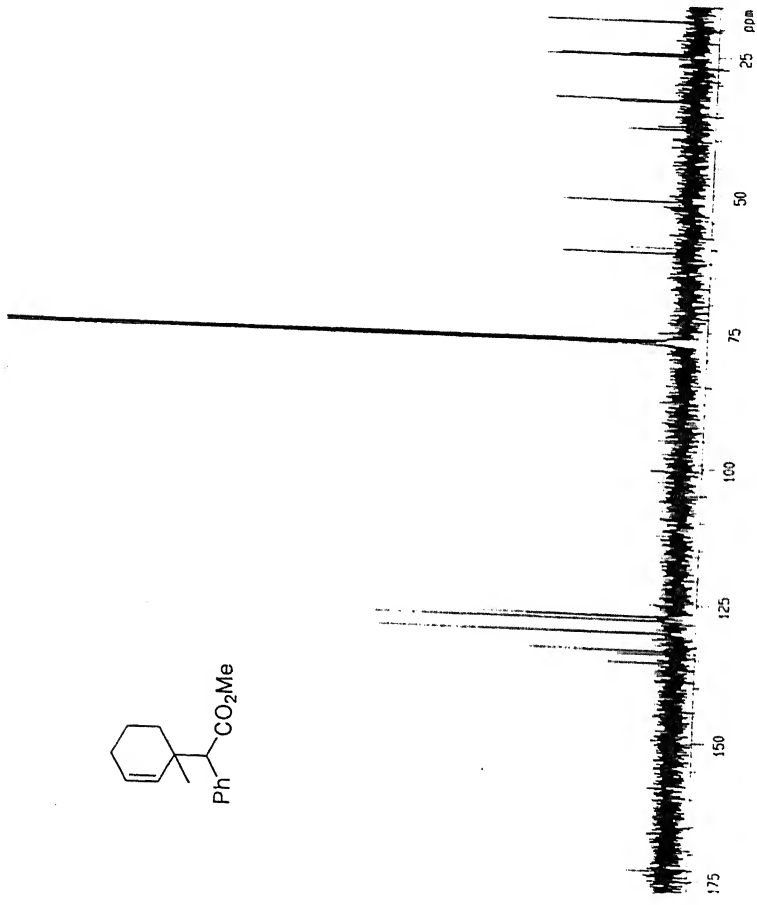


Figure 25. 100 MHz ^{13}C NMR spectrum of **64b**

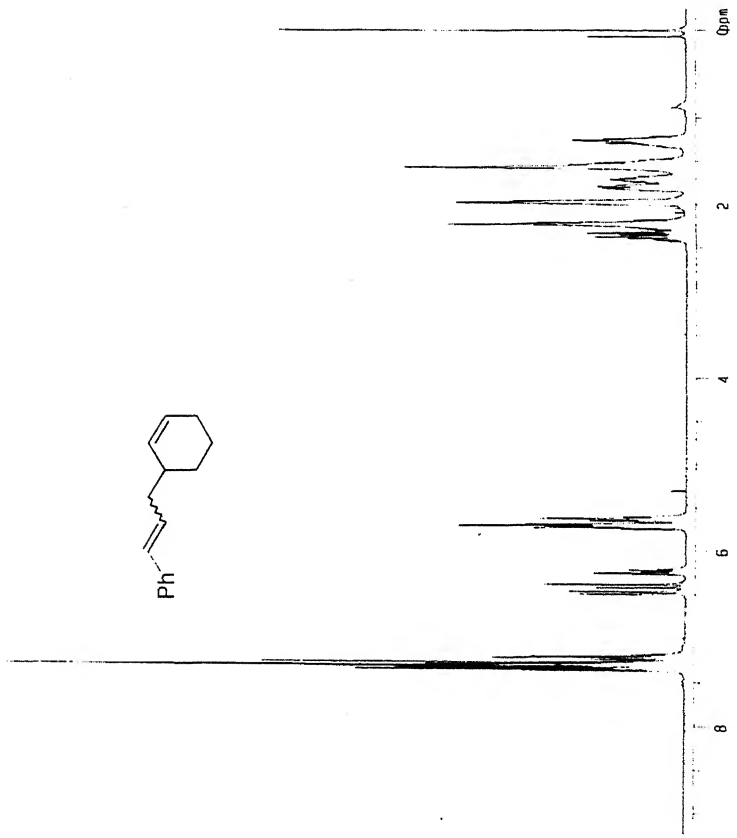


Figure 26. 400 MHz ^{1}H NMR spectrum of **66a**

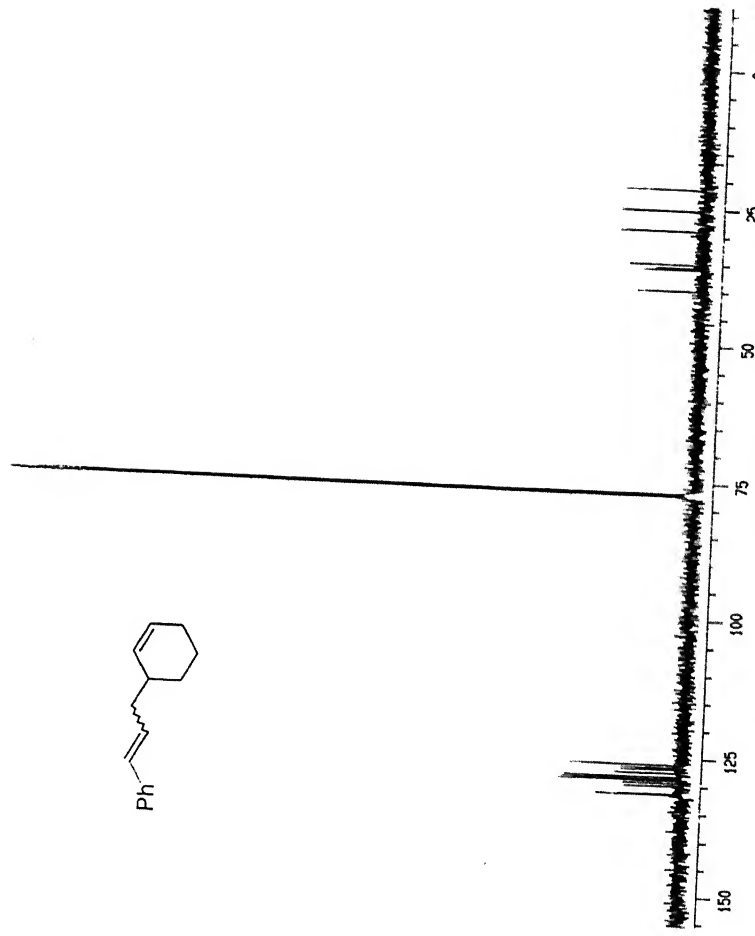


Figure 27. 100 MHz ^{13}C NMR spectrum of **66a**

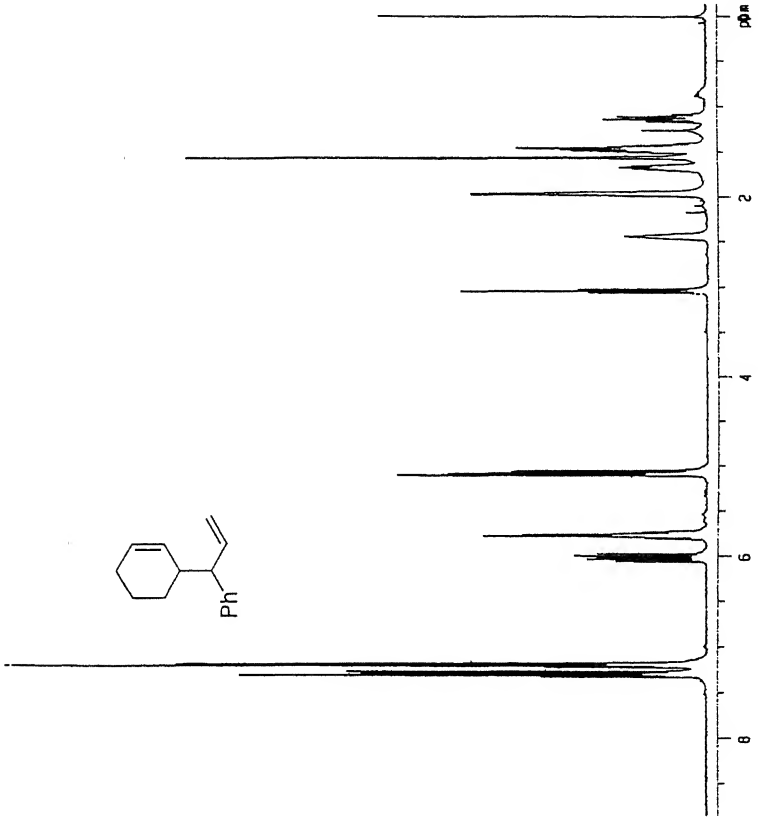


Figure 28. 400 MHz ^{1}H NMR spectrum of **66b** (less polar)

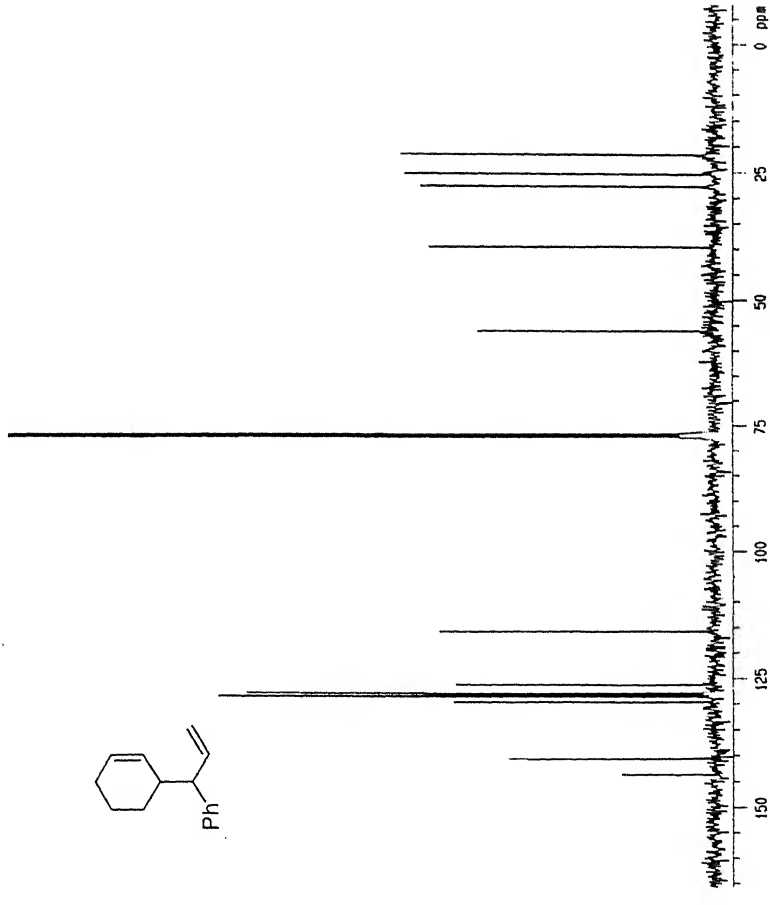


Figure 29. 100 MHz ^{13}C NMR spectrum of **66b** (less polar)

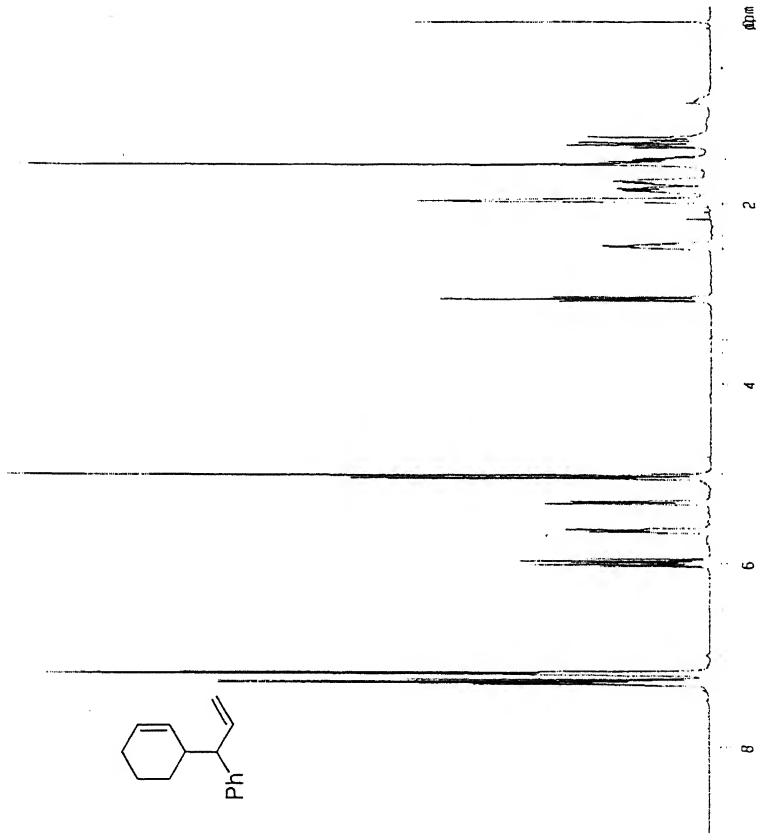


Figure 30. 400 MHz ^{1}H NMR spectrum of **66b** (more polar)

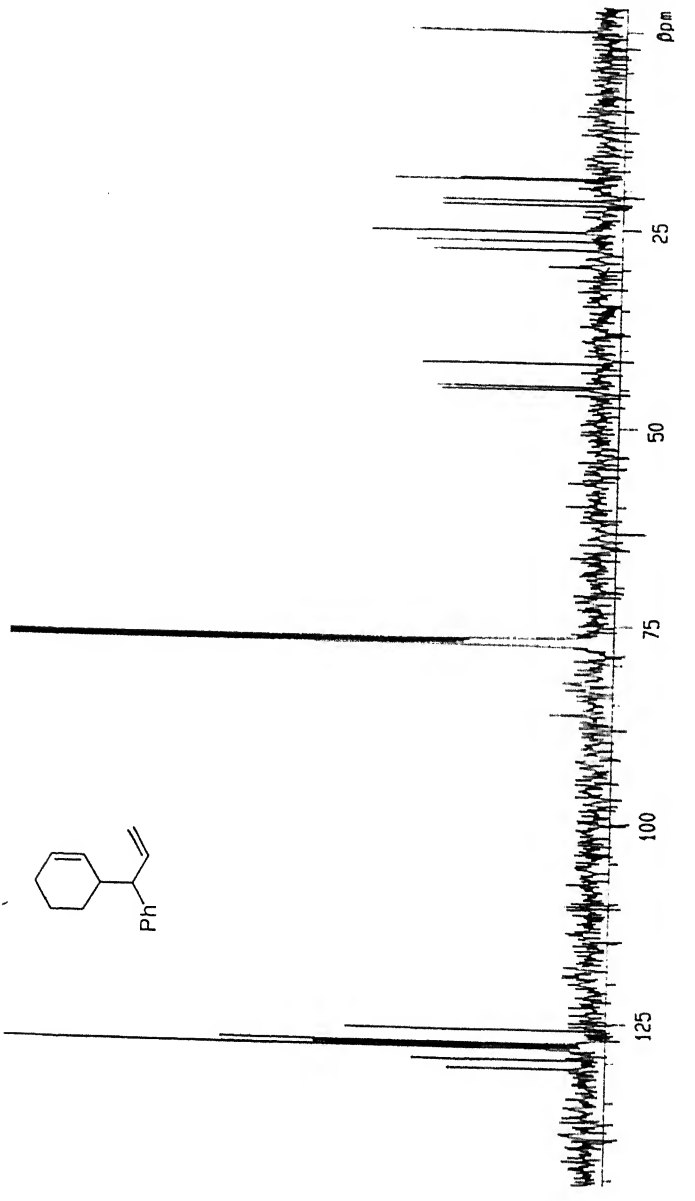


Figure 31. 100 MHz ^{13}C NMR spectrum of **66b** (more polar)

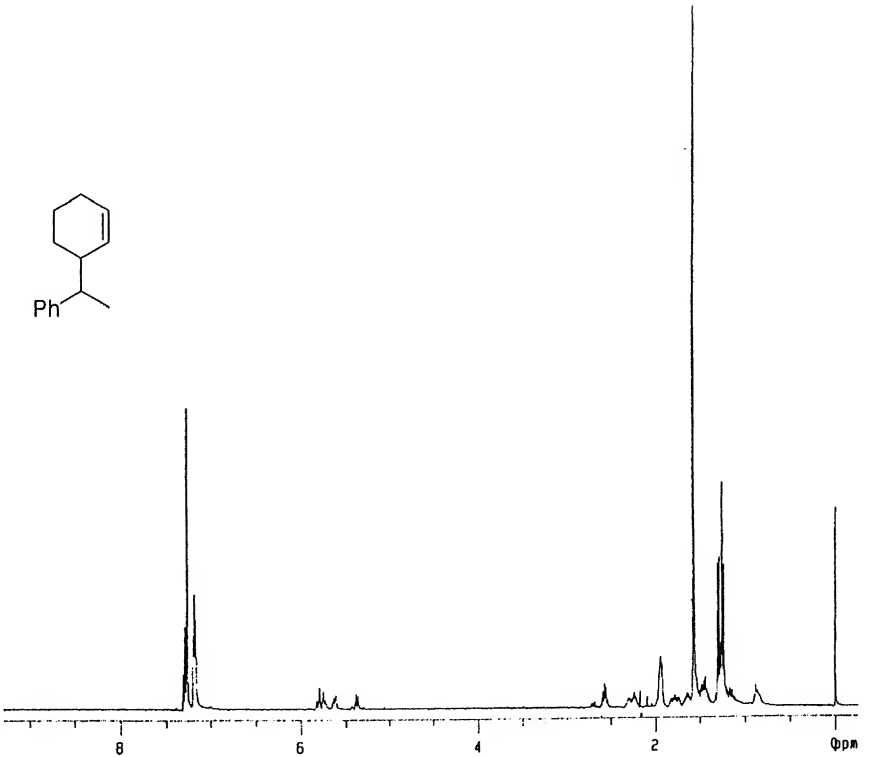


Figure 32. 400 MHz ^{1}H NMR spectrum of **67**

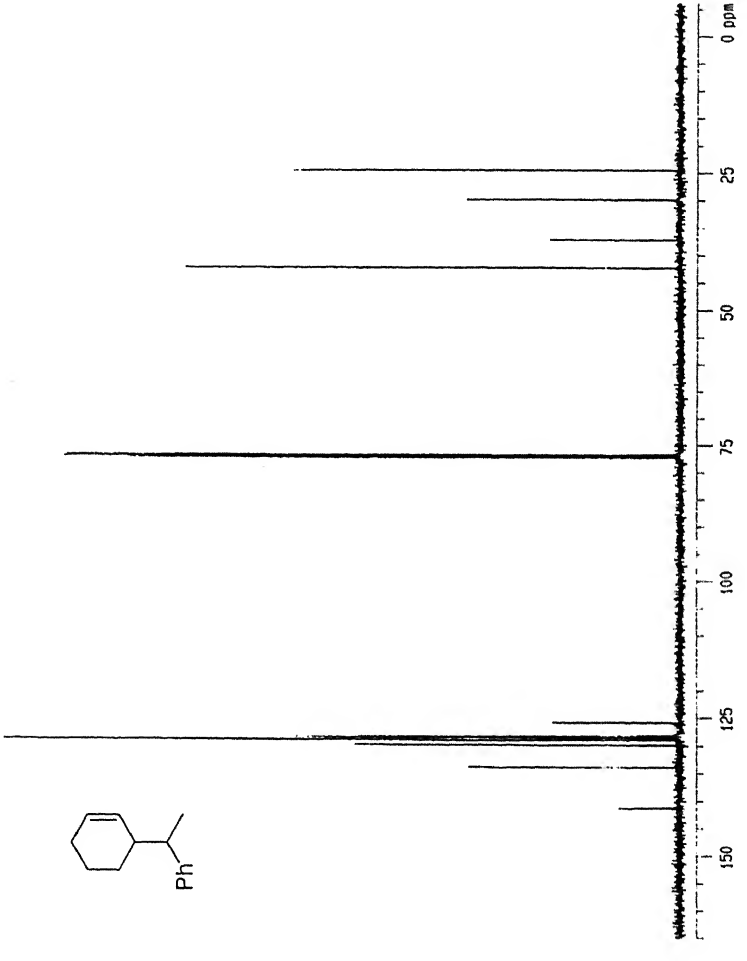


Figure 33. 100 MHz ^{13}C NMR spectrum of **67**

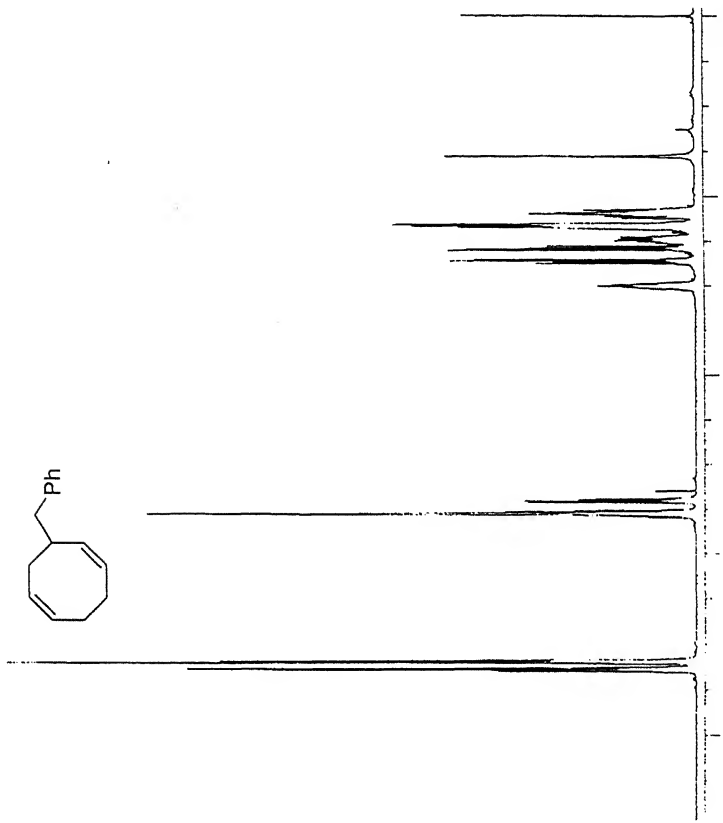


Figure 34. 400 MHz ^{1}H NMR spectrum of **68a** (more polar)

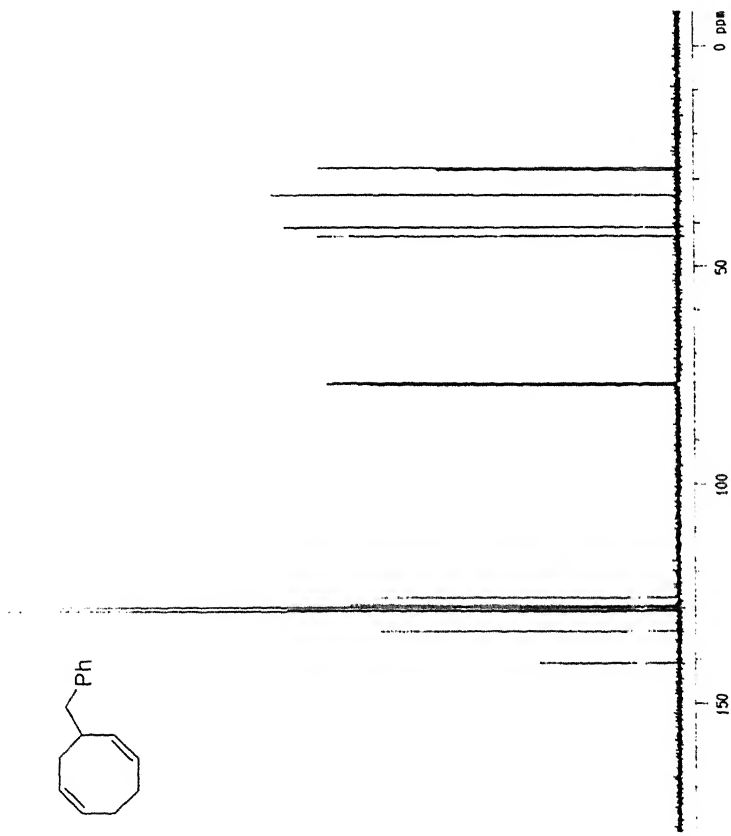


Figure 35. 100 MHz ^{13}C NMR spectrum of **68a** (more polar)

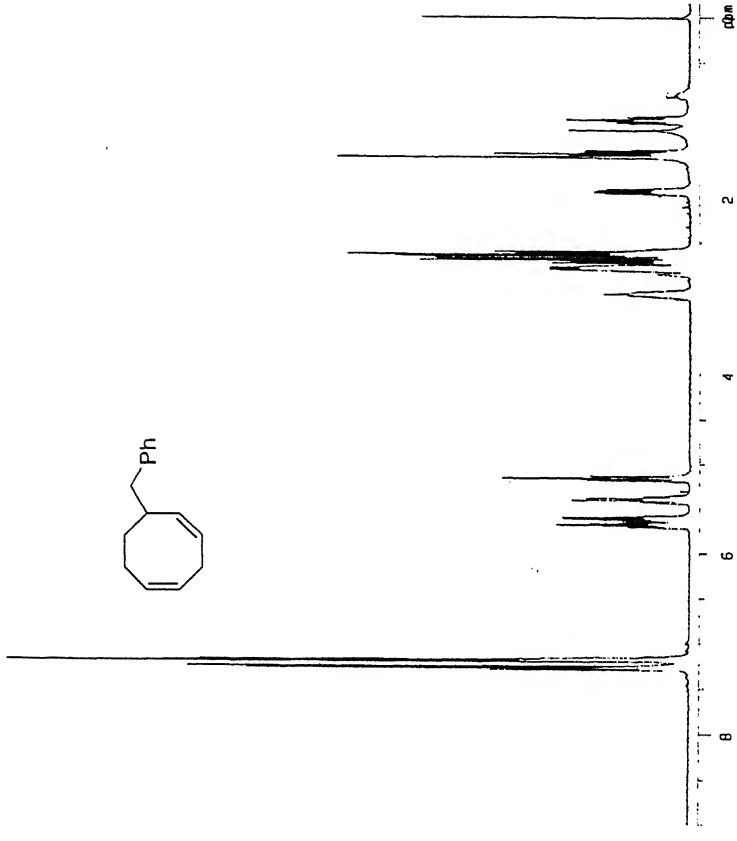


Figure 36. 400 MHz ^{1}H NMR spectrum of **68b** (less polar)

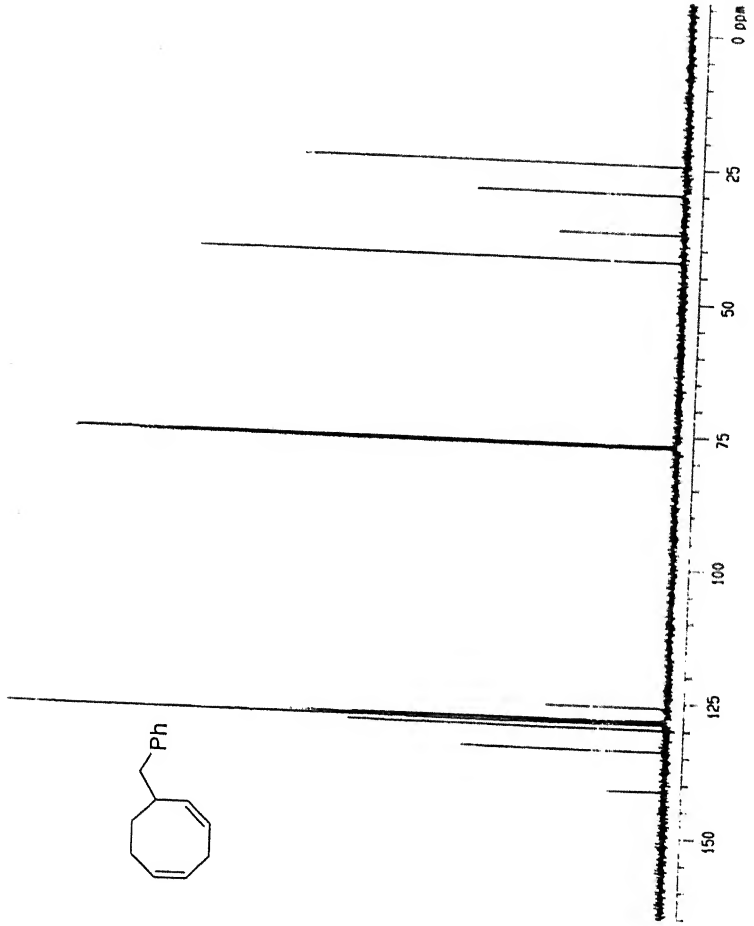


Figure 37. 100 MHz ^{13}C NMR spectrum of **68a** (less polar)

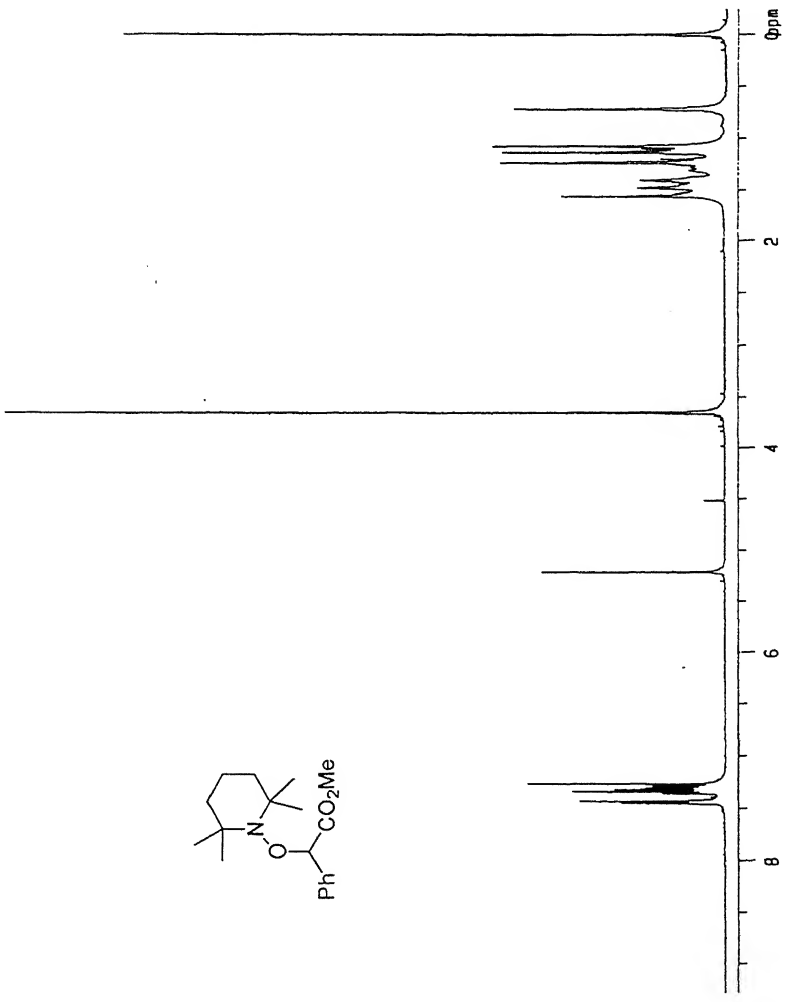


Figure 38. 400 MHz ^{1}H NMR spectrum of TEMPO adduct

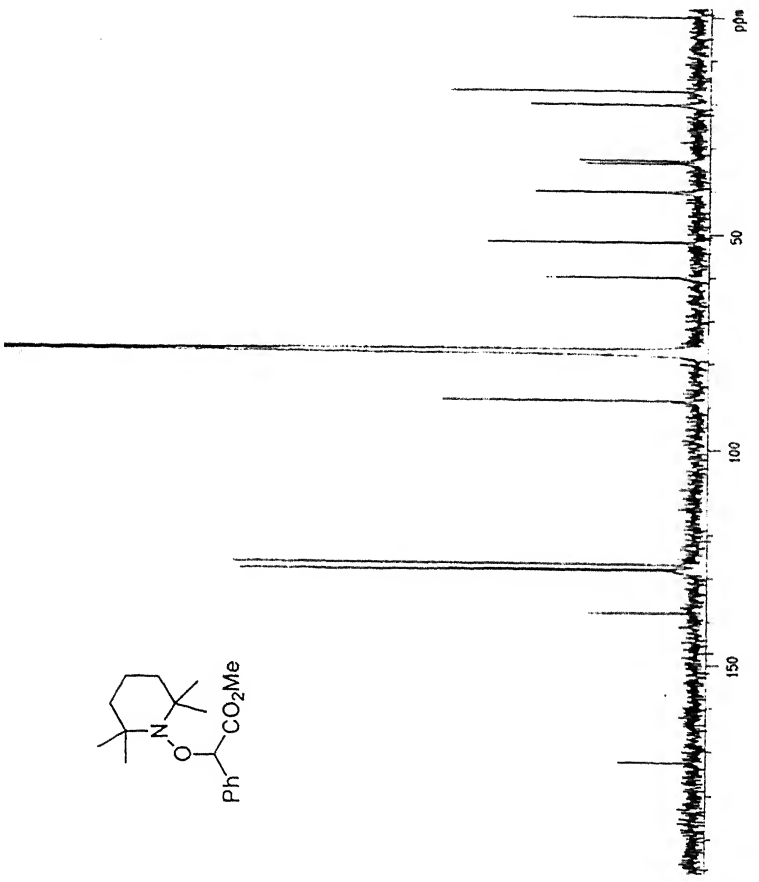


Figure 39. 100 MHz ^{13}C NMR spectrum of TEMPO adduct

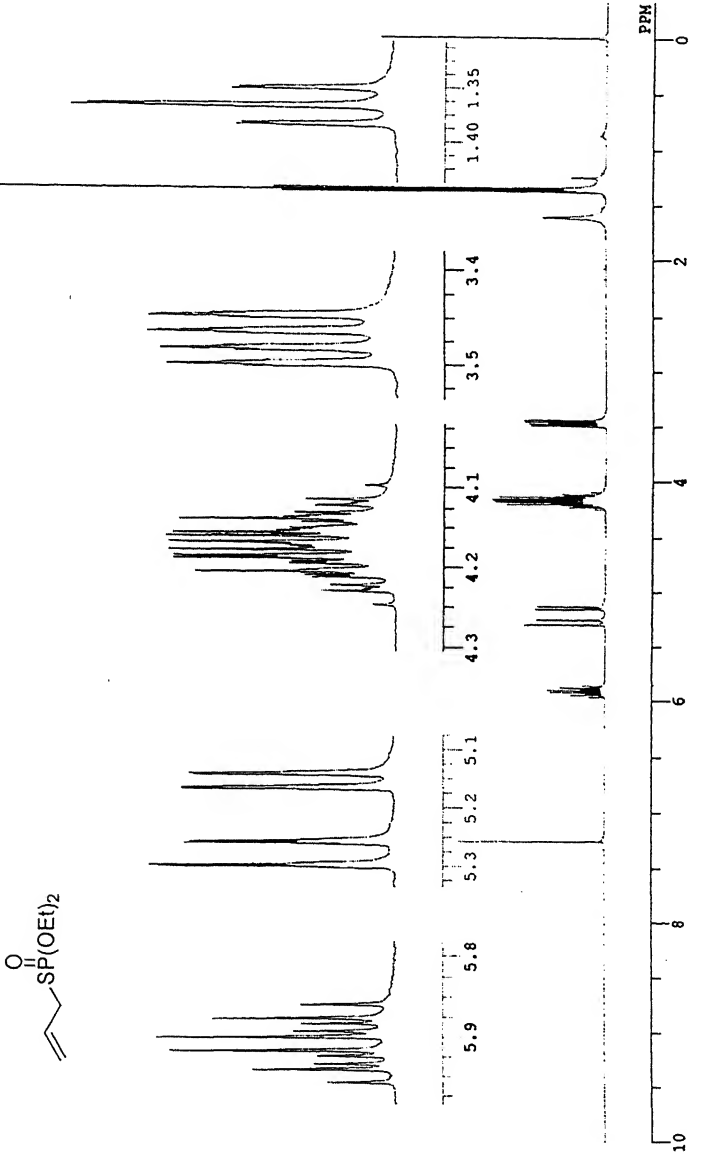


Figure 40. 400 MHz ^{1}H NMR spectrum of **72**

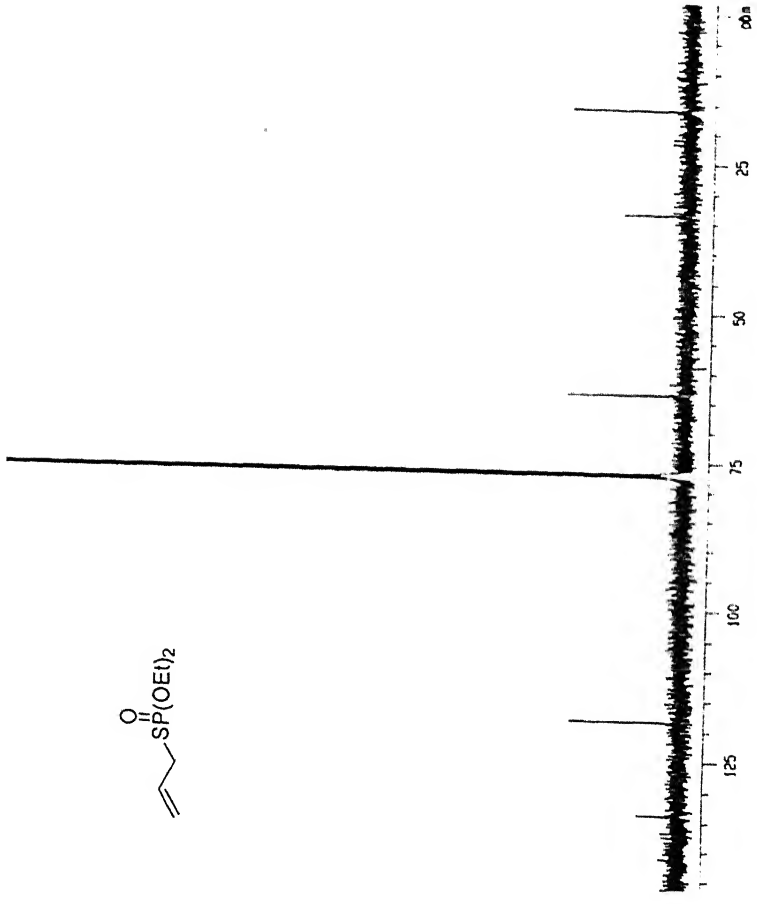


Figure 41. 100 MHz ^{13}C NMR spectrum of **72**

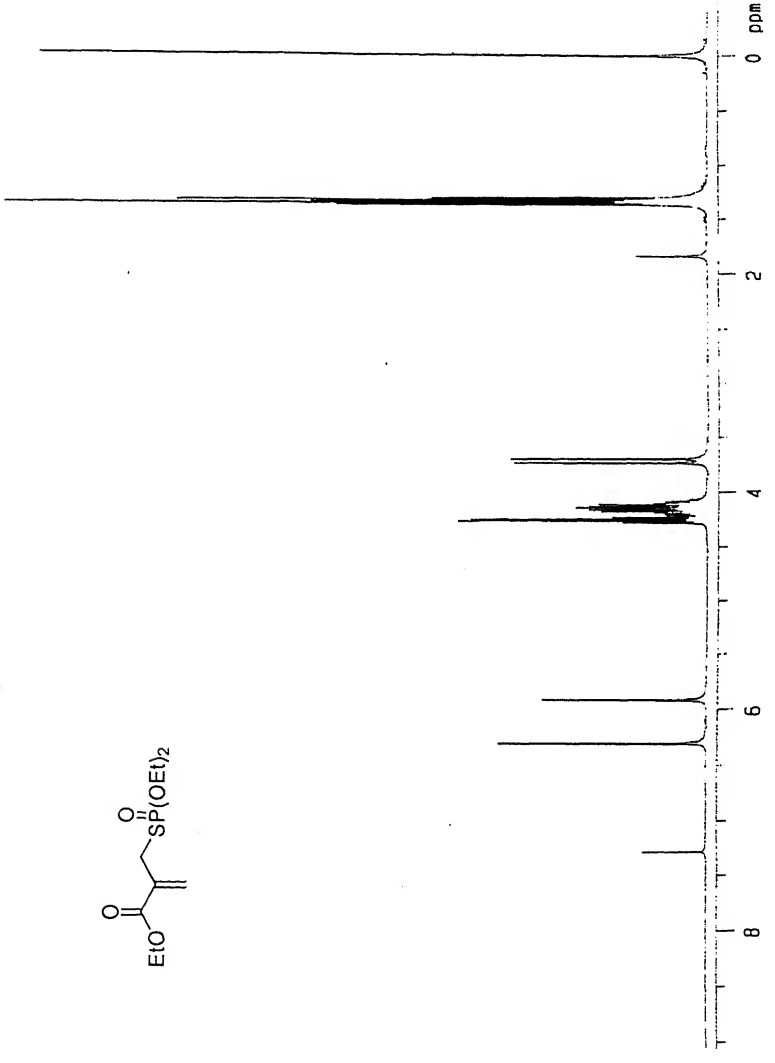


Figure 42. 400 MHz ^{1}H NMR spectrum of **75**

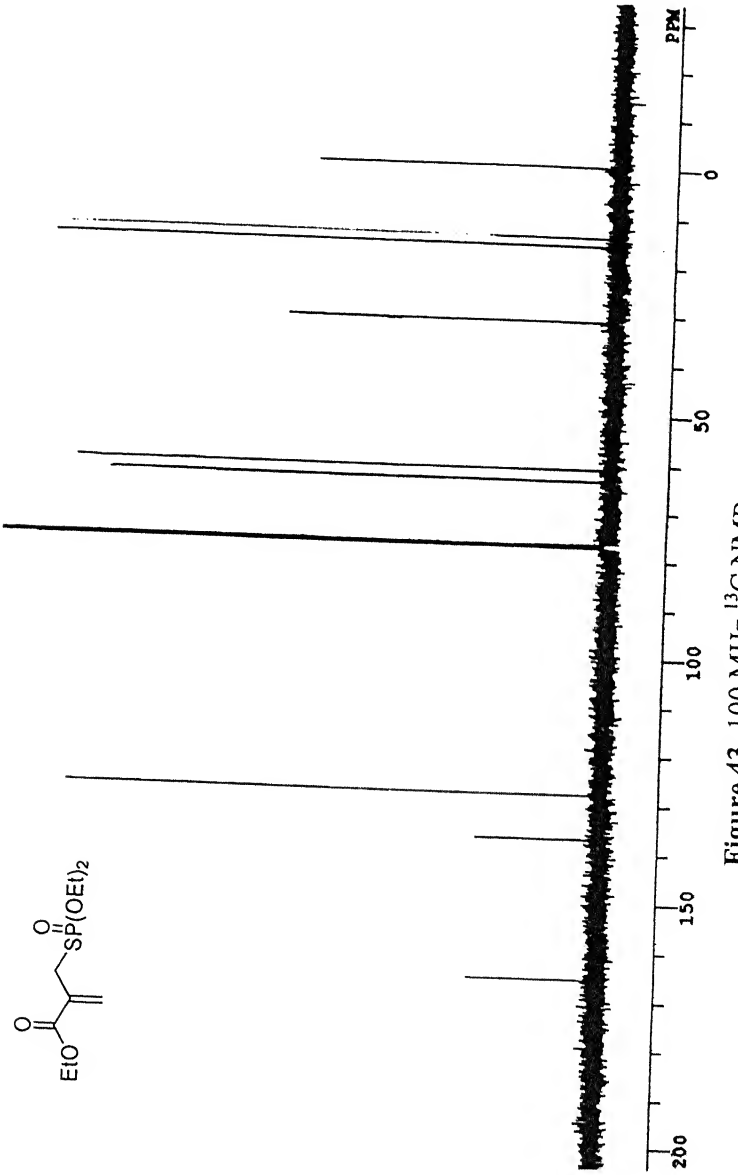


Figure 43. 100 MHz ^{13}C NMR spectrum of **75**

Chapter 3

Validity of the Rigid Conformer Concept in the Face Selection of Some Norbornan-7-ones Towards Nucleophilic Additions

3.1 Introduction

The discrimination of the two faces of a trigonal carbon towards nucleophilic additions has been a subject of intense debate ever since Cram proposed his model of diastereoselection.[1] It becomes important to look into various factors that contribute much to arrive at the desired target molecule with correct stereochemistry as most of the biologically and structurally important molecules possess well defined stereochemistry besides their molecular complexity. In the last two decades, the activity in this area has been remarkably high with a large number of systems studied, both experimentally and theoretically, to understand the nature of forces that govern the π-facial selection. From the studies on carefully designed substrates with sterically equivalent π-faces, many factors such as hyperconjugation, orbital, and electrostatic effects were also found to contribute to the observed selectivity in addition to the usual steric effects.

3.1.1 Diastereoselection in acyclic systems

In acyclic systems, the rotational freedom of the substituents makes the π-faces different in the transition state. Cram[2] proposed the first qualitative model **1** (Figure 1) to explain the stereoselectivity of

nucleophilic additions to acyclic carbonyl compounds. In the transition state, the carbonyl function is positioned antiperiplanar to the largest group, L, of the α-substituents to avoid the major destabilizing interactions between them; a nucleophile attacks from the direction *syn* to the smaller substituent, S. This model predicts the stereochemical outcome of nucleophilic reactions of most acyclic systems as long as there is no chelating or polar substituent present at the α-center. A heteroatom at the α-carbon forms a chelate with the carbonyl oxygen through a metal cation present in the nucleophile as shown in structure **2**. This allows the incoming nucleophile from the side of the smaller of the remaining substituents, leading to the product with stereochemistry different from the normal Cram product. A polar group at the α-center needs to play the role of the largest substituent to explain the facial selection by Cram model even when the molecule has other bulkier groups. Conforth,[3] in eliminating this failure of Cram model, considered that placing an electron withdrawing polar group antiperiplanar to the carbonyl group in the transition state should reduce the polar repulsions between them. The major drawback of Cram's model is that more importance was given to the carbonyl's bulk than to R-L interactions. Substrates containing considerably bulky R group will not prefer the transition structure **1** to avoid the destabilizing eclipsing interactions between R and L. This led Felkin[4] and Karabatsos[5] to refine the Cram transition state conformation.

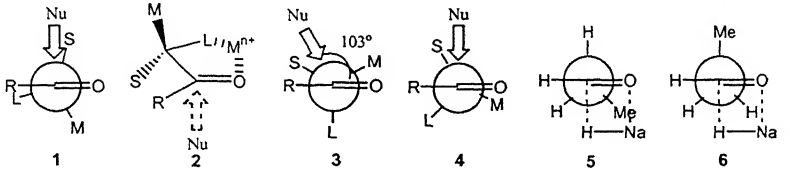


Figure 1. Predictive models for the nucleophilic additions to acyclic carbonyl compounds. 1. Cram model, 2. Cram chelation model, 3. Anh-Felkin model, and 4. Karabatsos model, 5 and 6. Houk model. S, M, and L represent, respectively, small, medium, and large groups and M^{n+} represents the metal cation

In nucleophilic additions to carbonyls, the trigonal carbon experiences sp^2-sp^3 hybridizational change during the course of the reaction. In the event, it develops a torsional strain in between the newly formed bond and the already existing bonds. In Felkin model, 3, L is placed orthogonal to the carbonyl π-plane and a nucleophile attacks from the direction opposite to L to eliminate this torsional strain. Anh's[6] theoretical calculations supported Felkin transition state conformation as the low-lying $\sigma^*_{C\text{-}L}$ orbital is stabilized by the antiparallel π and π* orbitals of the carbonyl function. Calculations also revealed that the nucleophilic attack does not take place orthogonal to the π plane but, rather, at 103° angle to the side of S to encounter minimum steric hindrance with the substituents at the α-center. Combining these individual concepts of Felkin and Anh, the model is named Anh-Felkin model. This model enjoys from the advantage that the product is formed directly in its staggered conformation.

In Karabatsos[5] proposal, the eclipsing interaction of L with R was considered to modify the Cram transition state conformation as in structure **4** and the attack is preferred from the least hindered side.

Houk's calculations supported Felkin-Anh model.[7] Houk considered the transition state in nucleophilic reactions is electron rich and a C-C bond as a better electron donor compared to a C-H bond. Calculations of the transition state structures for the addition of NaH to propanal revealed that the transition state **5** was favored over **6** as the orthogonal C-C bond in **6** destabilized the electron-rich transition state.

3.1.2 Diastereoselection in cyclic systems

Cyclic systems provide the best opportunity to evaluate the nature of various factors that play key roles in deciding the diastereoselection as the ground state conformation around the carbonyl group is fixed. Cyclohexanone, the simplest system in the series, preferred axial attack of hydrides even when it is less likely on steric grounds. Both the Cram and Karabatsos models, however, failed to account for this stereochemical change over. Consequently, several conceptual models were developed based on different effects. A brief account of some prominent models is presented in the following sections.

3.1.2.1 Models based on hyperconjugation effects

According to Felkin torsional strain model axial attack is favored in cyclohexanone systems as the nucleophile experiences torsional strain with the C2- and C6-axial-substituents in the equatorial attack.[4] In regard to the Anh's[6] model, the axial transition state is

favored by the better stabilization of the low lying σ* orbitals of the axial C2-H and C6-H bonds than those of the vicinal carbon-carbon bonds by the delocalization of electron density from the σ orbital of the newly formed C-Nu bond in axial and equatorial attacks, respectively (Figure 2). This attack, that is antiperiplanar to the vicinal σ bonds, has electronic origin and the arguments support an electron rich transition state. The knowledge of relative acceptor abilities of σ* orbitals of the vicinal bonds is needed to correctly predict the diastereoselectivity using this model. The role of a remote substituent cannot be comprehensively inferred from the Anh-Felkin model.

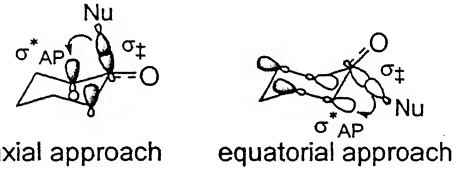


Figure 2. Stabilizing orbital interactions in Anh-Felkin model

Houk *et al.* [7] reported quantitative support to Felkin model for both cyclic and acyclic carbonyl compounds. Ab initio MO calculations were performed on various transition state geometries to arrive at the activation energies of LiH additions to different carbonyl compounds. They concluded that the Felkin model combined with the steric effects accounted for the stereochemical results from both the cyclic and the acyclic carbonyl compounds. Remote polar substituents such as OH and NH_2 exert long-range electrostatic effects on diastereoselectivity and are highly dependent on their orientations. The ratios obtained from

the torsional force constants for different transition state geometries directly correlated with the experimental selectivities of many systems.

Although the Anh-Felkin model explained the diastereoselectivities of many systems, certain valid points were not taken into account to make it more conceptual. For instance, care was not taken to include the eclipsing interactions in between the vicinal C2-C3 and C5-C6 bonds and the nucleophile during the axial attack. It is rather surprising that the torsional strain due to the axial C2- and C6-bonds during equatorial attack was solely responsible for the high axial preference.

In 1981, Cieplak claimed hyperconjugation (Figure 3) to have played a dominant role in overriding the intrinsic steric demands.[8] The incipient bond was considered stretched and polarized. Further, the p orbital of the carbonyl carbon was rendered electron deficient as a result of π-charge polarization induced by the approaching nucleophile and, thus, the hyperconjugative stabilization of the transition state was more in magnitude than that in the ground state. This hyperconjugative stabilization is conceptually opposite to Anh-Felkin model wherein the delocalization of electron density from the incipient bond to the low-lying σ^* orbitals was considered as the stabilization factor. The electron donating ability of a C-H bond was considered more than that of a carbon-carbon bond; the axial transition state was, thus, more stabilized. The relative order of donor abilities is C-S > C-H > C-C > C-N > C-O. The Cieplak model has been consistent with many of the

experimental results besides considerable disagreement[9,15] and criticism.[7,11,14]

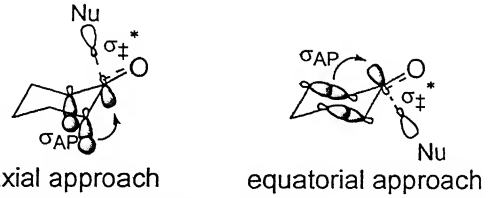


Figure 3. Stabilizing orbital interactions in the Cieplak model

3.1.2.2 Models based on orbital effects

The course of many chemical reactions has been explained by the interaction of specific occupied and unoccupied orbitals at the reaction site. It is obvious that the orbitals at the reaction site are distorted as the molecular orbital of any molecule is formed from the orbitals of the composite subsystems. This distortion allows one to arrive at the more probable reaction pathway.

Having this background, Klein[10] considered two molecular orbital mixing interactions between the β C-C bonds and the π-orbital of C=O in the ground state (Figure 4). The highest energy orbital in the bonding combination, HOMO, has an out-of-phase interaction of $\sigma_{C\text{-}C}$ lobes with $\pi_{C=O}$ lobes. This results in the diminishing of electron density on the axial face and increase of electron density on the equatorial face to favor electrophilic attack in exocyclic methylene molecules as a similar molecular orbital diagram could be drawn out on them. On the other hand, the in-phase-interaction in the low-lying molecular orbital of antibonding combination, LUMO, lowers the electron density of the axially oriented lobe. This allows better

interaction with the nucleophile in its axial attack. Klein's model lacks in not including the influences of remote substituents and the interactions of $\sigma_{C2\text{-}H}$ and $\sigma_{C6\text{-}H}$.

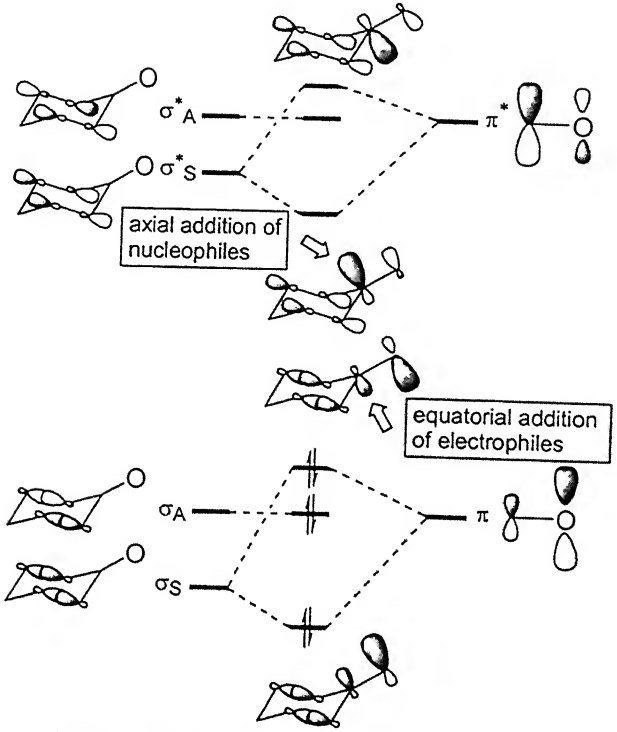


Figure 4. Orbital interactions in Klein model

Using Frontier Molecular Orbital theory (FMO), Frenking and co-workers[11] have rationalized the preferred diastereoselection of 3-F-cyclohexanones that could not be explained by the Cieplak model. The distortion of the frontier orbitals of the carbonyl carbon occurs during the interaction between the HOMO of the nucleophile and the $\pi^*_{C=O}$, LUMO, of cyclohexanone in an early transition state. Calculations of

the transition state energies for LiH addition revealed that the axial and equatorial transition states were favored for 3-*eq*-F- and 3-*ax*-F-cyclohexanones, respectively. This model has not been verified in significant number of systems whose selectivities are well documented to trust its reliability.

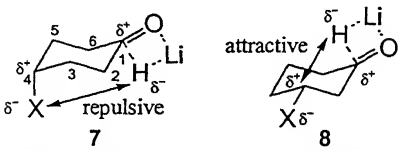
Dannenberg[12] developed Polarized π-Frontier Molecular Orbital (PPFMO) theory that considers the polarization of the antisymmetric p orbital on the carbonyl carbon and is obtained by the superimposition of two new s functions on either face at a distance that results in maximum effect. A MO calculation is performed on the added Gaussian functions whose coefficients are varied freely. The polarization, *p,* is obtained by the algebraic sum of the coefficients. The sign of the polarization indicates the side the polarization has occurred and it is used to predict the diastereoselectivity. Like the Cieplak model, PPFMO model failed to explain the preferred equatorial attack in 3-*ax*-F-cyclohexanone.

Exterior Frontier Orbital Extension (EFOE) model is a recently developed model by Tomoda[13] that basically considers two important terms of the Salem-Klopman equation that express the kinetic driving force for a chemical reaction. Tomoda considers the two factors, namely, π-plane divided accessible space (PDAS) and π-plane-divided exterior frontier orbital electron density (EFOE) as the major contributors to the observed selectivity. Both PDAS and EFOE are calculated using three-dimensional lattice method at HF/ 6-31* level with a unit cube of 0.001~0.008 au^3 (1.48×10^{-4}~1.18×10^{-3} $Å^3$) up to a

limit of 5 au (2.65 Å) above the molecular surface on either face of the π system. Tomoda has interpreted the stereochemical outcome of nucleophilic additions to substituted cyclohexanones, heterocyclohexanones, other cyclic ketones, imines, and iminium ions by combining the parameters PDAS and EFOE. This model requires too many computation steps to arrive at results.

3.1.2.3 Models based on electrostatic effects

Several research groups have stressed the importance of electrostatic effects in the discrimination of π-faces and often insisted that the Cieplak's transition state hyperconjugative model is less meaningful in many systems. Houk and co-workers have explained the experimental results obtained from the nucleophilic additions to many cyclic ketones by invoking electrostatic effects.[7,14] The diastereoselectivities are highly dependent on the orientation of the polar substituent and the solvent used. For example, axial electron-withdrawing substituents on C4 in 7 (Figure 5) destabilize equatorial attack by electrostatic repulsive interactions; the axial attack, therefore, is favored. Since an axial electron-withdrawing substituent on C4 cannot alter much the electron-donating abilities of the C2-C3 and C5-C6 bonds than an equatorial electron-withdrawing group, Cieplak model is not applicable. Similarly, an electron-attracting equatorial substituent on C3 in **8** induces a positive charge on C3, which stabilizes a negatively charged nucleophile upon axial attack. With similar arguments, Houk explained the stereochemical outcome of several systems.



7 8

Figure 5. Electrostatic interactions according to Houk

Wipf and co-workers[15] have studied α- and β-selectivities of 4,4-disubstituted cyclohexadienones (Figure 6). Several similar 4,4-disubstituted cyclohexadienones showed similar *anti* to electron withdrawing group selectivities to organometallic reagents that cannot be explained by transition state hyperconjugation model. Wipf correlated the dipole moment perpendicular to the dienone moiety with the observed selectivities. The net dipole moment due to the C4-functional group was calculated with the semiempirical AM1 method. The vector components of the dipole moments perpendicular to the dienones ($\mu_{\perp}$) showed a linear relationship with the natural logarithm of the experimentally observed selectivities. An increase in selectivity in solvents of higher dielectric constants was explained by the increase in the perpendicular dipole moment of the substrate induced by the medium. However, polar solvents with high dielectric constants are, in fact, expected to reduce the dipole-dipole or dipole-point charge interactions in between the reactants and, hence, the effect due to increase in solvent polarity is not precisely predictable.[15] Also the solvent polarity has influence on the aggregation state of the organometallic reagent.[15] Thus, more studies are required to generalize the actual role of solvents in these systems.

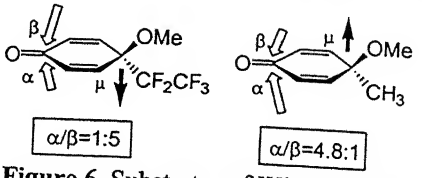


Figure 6. Substrates of Wipf's model

Chandrasekhar and Mehta developed a model to gain better insights concerning the relative contributions of different factors to nucleophilic additions to sterically unbiased systems.[16] They considered the electrostatic and orbital effects separately. Here, the electrostatic interactions due to an approaching nucleophile were modeled by placing a point charge above and below the π plane using the "sparkle" option of the MOPAC program. Approximating a point charge for hydride did not provide a quantitative evaluation of the electrostatic effects in real sense. This is because a point charge is harder and will show a greater effect than hydride. Their calculations with a test charge of −0.5 on selected substrates showed the same trend as that observed with the point charge, revealing thus the importance of the electrostatic effects. Secondly, a hydride ion was approximated for nucleophile to include the electronic effects. Calculations similar to those as above were performed on substrates with hydride ion in the place of the point charge. These calculations include the orbital interactions between the nucleophile and the carbonyl compound. Thus, the charge and the hydride models in combine, make semiquantitative approach to evaluate the electrostatic *vs.* orbital effects in face preferences. This model explained the observed selectivities of many polycyclic ketones with a few exceptions.

3.1.2.4 Complexation model

Cation complexation has played a dominant role for the structure and reactivity changes in many organic reactions and biological processes. Many experimental findings insist that the nucleophilic additions to a carbonyl function are generally preceded by the complexation of the counter cation with the carbonyl oxygen and it occurs in the σ-plane of the carbonyl function. Many of the models discussed in the previous sections have not taken this important complexation process into account. Houk model assumes the simultaneous approach of both the components, the cation and the anion, of the nucleophile to the carbonyl π-plane and, thus, it ignores the well-documented cation-carbonyl complexation and the consequent geometrical changes in the molecule.

Royer, using CNDO method indicated that the most favored approach channel was oriented towards the axial direction in a lithium-complexed cyclohexanone.[17] Also, the energy obtained on including the polarization and charge transfer factors for the axial approach (-1887.63 eV) was lower than that for the equatorial approach (-1886.12 eV). Hence, an axial attack was proposed on electrostatic considerations.

The complexation will reduce the C=O bond order and alter the torsion angles of the carbonyl oxygen with the ring positions. These torsion angle changes are, in turn, dependent on the nature, orientation, and relative position of a ring substituent relative to the carbonyl function. Moreover, the reduction in C=O bond order after

complexation causes pyramidalization at the carbonyl carbon and enlarges the coefficient of the empty p_z orbital of the carbonyl carbon which must orient *anti* to the more electron releasing vicinal bond (Figure 7). Also, the complexation causes significant geometrical changes around the carbonyl carbon so that the molecule acquires maximum conformational stability in accordance with the stereoelectronic effects.

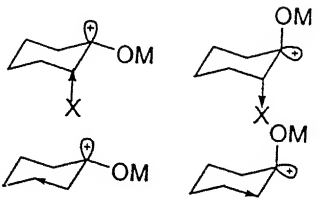


Figure 7. Stereoelectronically favored axial and equatorial orientations of the empty p-orbital on cation complexation. The head of the arrow indicates the direction of electron flow along the bond. M = cation and X = substituent

Many experimental findings are in favor of the above argument. The crystal structure analysis of the complex 5-Phenyladamantan-2-one-pentachloroantimony has revealed a better hyperconjugative interaction in the complexed form than the ground-state uncomplexed adamantanone.[18] Stereoelectronic effects favor a situation wherein an electron poor orbital is oriented antiperiplanar to an electron rich bond or an electron pair orbital as the resultant donor-acceptor interaction makes the system thermodynamically more stable. More direct supports for the antiperiplanar stabilization of the electron poor orbital come from the studies of Adcock.[19] From studies on the

nucleophilic capture of the intermediate 5-substituted-2-adamantyl cation **10a/10b**, generated from **9** (Figure 8), by Cl^- and F^-, Adcock established the dependence of selectivity on the nature of the substituent. Both the epimeric alcohols resulted in the same products distribution, suggesting a common carbocation intermediate. An electron-donating group facilitated the formation of **10a** by antiperiplanar stabilization and, thus, an *anti*-approach of a nucleophile was favored.

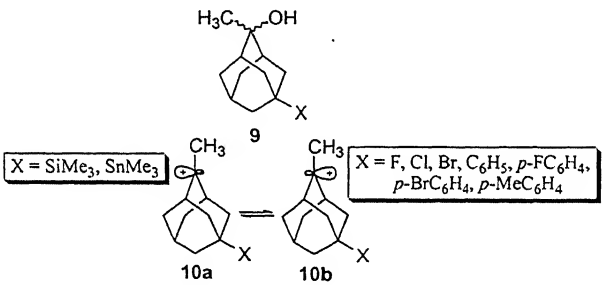


Figure 8. Preferred face selection in the capture of 2-adamantyl cation generated from 5-X-2-methyladamatan-2-ol by Cl^- and F^-

From yet another study of Adcock *et al.*,[19] the results of the hydride trapping of the species **12** for a series of substituents exerting different electronic effects are consistent with the importance of antiperiplanar stabilization of the electron poor orbital by the σ-donor substituents. The species **12** was generated *in situ* from **11** (Figure 9). The observed selectivities were less compared to the selectivities observed from Cl^-/F^- trappings of the 5-substituted adamantyl cations above. This has been explained in terms of less electron-demand at the reaction center caused by the powerful π-electron-donating methoxy

group on C2. The need for electron-demand at the reaction center for better antiperiplanar stabilization has been highlighted from the $NaBH_4$, $LiAlH_4$, and DIBAL-H reductions of selected 5-X-adamantanones (X = F, Br, $SiMe_3$, $SnMe_3$).[19] The substrates with $SiMe_3$ and $SnMe_3$ substituents that are not selective with $NaBH_4$, showed slight *anti*-selectivity with $LiAlH_4$ and DIBAL-H. This interesting result is, however, due to the increase in electron-demand at the carbonyl carbon on complexation of the carbonyl oxygen with the Li of $LiAlH_4$ and DIBAL-H. This is evident from the comparatively better selectivities obtained from hydride reduction of the oxacarbenium ion **12** that is equivalent to Me^+-complexed adamantanone. Adcock concluded by stating, "the selectivities of ketone reduction could be enhanced by increasing the electron demand of the reaction center by complexing the carbonyl oxygen with cations".

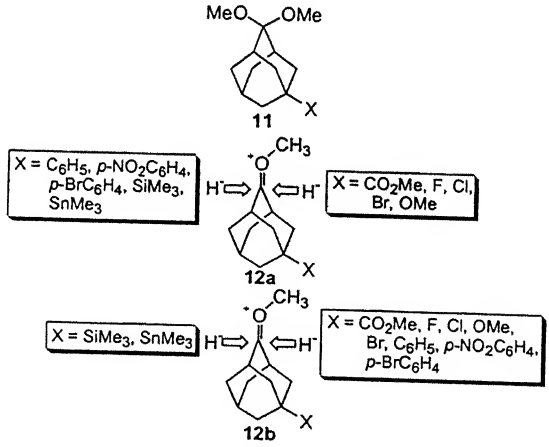


Figure 9. Preferred face selection in the hydride trapping of oxacarbenium ion generated *in situ* from 2,2-dimethoxy-5-X-adamantanes. **12a** and **12b** correspond, respectively, to the reductions using Et_3SiH and $PhSiH_3$

More recently Yadav and co-workers[20] have carried out ab initio MO investigation to compute the geometrical changes that occurred on cation complexation to explain and predict the stereochemical outcome of nucleophilic additions. This approach constitutes a simple but more conceptual as it is fully supported by the stereoelectronic effects. More importantly, it makes no assumptions of any sort as most other models do and it also avoids the much painful transition state calculations. Using this approach, systems such as **13-19** (Figure 10) were studied and their selectivities predicted correctly.

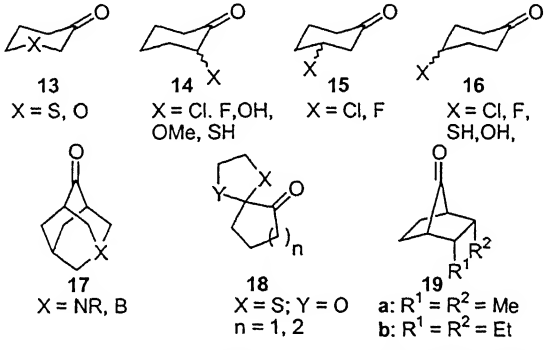


Figure 10. Structures of different systems studied using cation complexation model

3.2 Present work

3.2.1 Facial selectivity of norbornan-7-ones

Norbornan-7-ones have been the subject of intense experimental studies for their facial selectivities caused by *endo*-substituents at positions 2 and 3. Unlike cyclohexanones, norbornan-7-ones are rigid and devoid of significant geometrical distortion around the carbonyl function. Mehta and co-workers have studied the effects of endo substituents on the facial selectivities of many substituted

norbornan-7-ones **19** norbornen-7-ones **20** (Figure 11).[21] They explained the observed selectivities in most of the systems with the charge model (*vide infra*).[16] Orbital effects obtained by approximating hydride are either small or reinforce electrostatic effects in these systems.

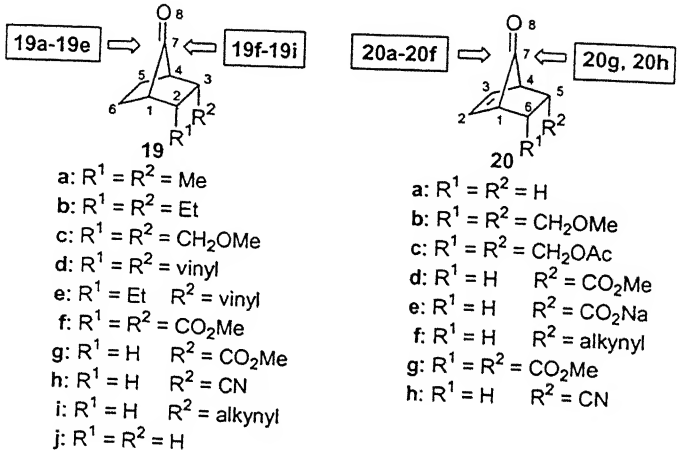


Figure 11. Observed facial preferences in *endo*-substituted norbornan-7-ones **19** and norbornen-7-ones **20**

The behaviors of the systems **19c** and **19d** towards nucleophilic additions are interesting. These substrates show *anti*-preference for the addition of nucleophiles despite being traditionally considered as electron attracting (*-I*) groups. Mehta[21] and le Noble[22] have attributed the observed *anti*-selectivities to through space donations from these substituents in rigid conformers such as **21** (Figure 12) for the divinyl species. The vinyl π bonds are held parallel to the C1-C2 and C3-C4 bonds.

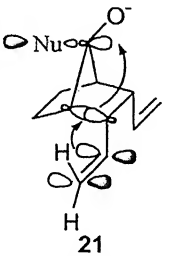


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Figure 12. Proposed rigid conformer of **19d**

From the transition state structures for LiH additions to a series of 2,3-disubstituted-7-norbornanones, Houk and co-workers[14c] have concluded that the hyperconjugation effects are less important than the electrostatic effects for the control of diastereoselection. Electron-withdrawing substituents induced positive charge on C2/C3 and the *syn*-attack was favored. Likewise, electron-donating substituents induced negative charges on C2/C3 and the *anti*-addition was favored. This rationale, however, is qualitatively against the *anti*-selectivities showed by **19c** and **19d**. Houk and co-workers considered the hydroxymethyl and vinyl groups as weakly electron donating to explain the observed selectivity against the well-accepted fact that these groups are electron-withdrawing in nature.

Though the rigid conformer concept may appear logical, it nevertheless prompted us to employ the cation complexation model to evaluate its applicability to these systems and also to test the merits of the rigid conformer concept.

3.2.2 Results and discussion

In application of the cation complexation model to norbornan-7-ones, we calculated the torsion angles D1 = O8-C7-C1-C2, D2 = O8-

C7-C1-C6, D3 = O8-C7-C4-C3, and D4 = O8-C7-C4-C5, both before and after complexation, to assess the direction of carbonyl pyramidalization. The pyramidalization is '*anti*' when D1 and D3 are smaller than D2 and D4 and '*syn*' when D1 and D3 are larger than D2 and D4. The '*anti*-pyramidalization' leads to *anti*-addition and the '*syn*-pyramidalization' leads to *syn*-addition. These geometrical data are collected in Table 1, the relevant *app*-effects in Table 2 and the 3D geometries of **19c**, **19d**, and **19f** in Figure 13.

Table 1. Selected B3LYP/6-31G* geometrical parameters of **19c**, **19d** and **19f** and their complexes. D1 = O8-C7-C1-C2; D2 = O8-C7-C1-C6; D3 = O8-C7-C4-C3; D4 = O8-C7-C4-C5

Substrate	D1	D2	D3	D4
19j	124.56	-124.56	-124.56	124.56
19c	122.29	-124.50	-121.49	125.08
19c-H^+	115.56	-132.55	-114.70	132.56
19c-Li^+	119.50	-127.88	-119.66	127.33
19d	121.31	-125.33	-121.31	125.33
19d-H^+	112.13	-135.90	-112.85	135.20
19d-Li^+	119.16	-128.15	-119.13	128.19
19d-BH_3	120.48	-126.71	-120.42	126.46
19f	125.10	-121.76	-122.35	124.79
19f-H^+	127.39	-120.03	-123.95	123.96
19f-$2H^+$	133.32	-111.84	-132.66	115.05
19f-$2Li^+$	127.12	-119.98	-126.78	120.15

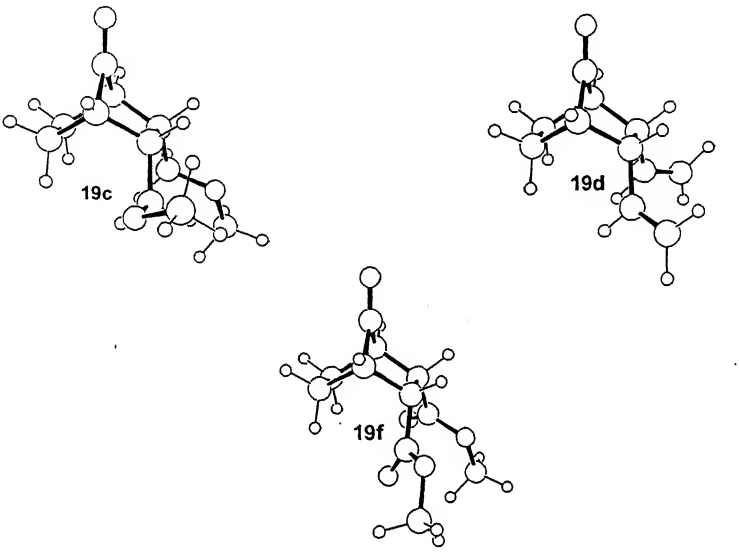


Figure 13. Computed 3D structures of **19c**, **19d** and **19f**

The torsion angle changes in **19c** and **19d** on carbonyl protonation suggest *anti*-addition for both. This is in accordance with the experimental observations.[21] From reactions with $NaBH_4$ in MeOH and MeLi in Et_2O, 40:60 and 34:66 and 36:64 and 27:73 selectivities in favor of *anti*-addition were observed for **19c** and **19d**, respectively. We sought a rationale for this *anti*-preference in the orientations of the substituents and their *app*-interactions with $\sigma^*_{C1\text{-}C2}$ and $\sigma^*_{C3\text{-}C4}$. Whereas the CH_2-O bond on C2 is *app* to C2-C3 (O-C-C2-C3 = 170.99-175.00°), the CH_2-O bond on C3 is *app* to C3-C4 (O-C-C3-C4 = 168.97-171.97°). The sum of the $\sigma_{C1\text{-}C2}$-$\pi^*_{C=O}$ and $\sigma_{C3\text{-}C4}$- $\pi^*_{C=O}$ and of the $\sigma_{C1\text{-}C6}$- $\pi^*_{C=O}$ and $\sigma_{C4\text{-}C5}$- $\pi^*_{C=O}$ interactions are, respectively, 6.84 and 6.56 kcal mol^{-1} in **19c**, 17.60 and 11.20 kcal mol^{-1} in **19c**-H^+,

and 11.97 and 9.04 kcal mol^{-1} in **19c**-Li^+. The better interactions of $\pi^*_{C=O}$ with σ_{C1-C2} and σ_{C3-C4} in comparison to the interactions with σ_{C1-C6} and σ_{C4-C5} are set to favor *anti*-pyramidalization and, hence, the observed *anti*-addition. It is interesting to note that one of the two C-H bonds of the methylene on C2 is *app* to C1-C2 (H-C-C2-C1 = 171.07-174.43°) and the σ_{C-H}-σ^*_{C1-C2} interaction energy is 3.61, 4.02 and 3.98 kcal mol^{-1} in **19c**, **19c**-H^+, and **19c**-Li^+, respectively. These arguments are inline with our rationale to explain the *anti*-selectivities of **19a** and **19b**.[20g] Converse to the observed *anti*-selectivity, Cieplak model predicts *syn*-selectivity since it considers σ_{C-H} a better donor than σ_{C-C}. The interesting feature is the observation that in contradiction to the hypothesis of le Noble and Mehta, neither σ_{C-O} nor any of the electron pair orbitals on oxygen is in interaction with σ^*_{C1-C2}.

Table 2. The B3LYP/6-31G* *app*-effects from second order perturbation theory analysis of the Fock matrix in NBO basis for **19c**, **19d** and **19f** and their complexes

Substrate	E/kcal mol^{-1}			
	σ_{C1-C2}-π^*_{C7-O8}	σ_{C1-C6}-π^*_{C7-O8}	σ_{C3-C4}-π^*_{C7-O8}	σ_{C4-C5}-π^*_{C7-O8}
19c	3.46	3.41	3.38	3.15
19c-H^+	9.65	5.76	7.95	5.44
19c-Li^+	6.36	4.56	5.61	4.48
19d	3.64	3.08	3.64	3.08
19d-H^+	10.0	4.67	10.1	4.75
19d-Li^+	6.27	4.31	6.28	4.30
19d-BH_3	4.93	3.94	4.81	3.78
19f	3.13	3.44	3.76	3.08
19f-H^+	6.21	7.40	8.02	6.38
19f-$2H^+$	4.60	6.92	5.91	7.57
19f-$2Li^+$	4.37	4.89	4.45	4.82

The sums of $\sigma_{C1\text{-}C2}$-$\pi^*_{C=O}$ and $\sigma_{C3\text{-}C4}$-$\pi^*_{C=O}$ and $\sigma_{C1\text{-}C6}$-$\pi^*_{C=O}$ and $\sigma_{C4\text{-}C5}$-$\pi^*_{C=O}$ interactions are 7.28 and 6.16, 20.1 and 9.42, 12.55 and 8.61, and 9.74 and 7.72 kcal mol^{-1} in **19d**, **19d**-H^+, **19d**-Li^+ and **19d**-BH_3, respectively. The larger interactions of $\pi^*_{C=O}$ with $\sigma_{C1\text{-}C2}$ and $\sigma_{C3\text{-}C4}$ compared to its interactions with $\sigma_{C1\text{-}C6}$ and $\sigma_{C4\text{-}C5}$ favor *anti*-pyramidalization. Both the vinyl groups are in an eclipsing orientation with the *exo*-hydrogens on C2 and C3. The $\pi_{C=C}$-$\sigma^*_{C1\text{-}C2}$/$\pi_{C=C}$-$\sigma^*_{C3\text{-}C4}$ interaction energy is 3.50, 5.20, 4.42, and 3.84 kcal mol^{-1} in **19d**, **19d**-H^+, **19d**-Li^+ and **19d**-BH_3, respectively. These interactions raise the electron densities of $\sigma_{C1\text{-}C2}$ and $\sigma_{C3\text{-}C4}$ in support of the earlier speculations.[21, 22]

From the absolute values of D1/D2 and D3/D4 in **19f**, one experiences great difficulty in predicting the facial selection. While D1 is larger than D2 by 3.34°, D3 is smaller than D4 by 2.44°. Since the sum of the $\sigma_{C1\text{-}C2}$-$\pi^*_{C=O}$ and $\sigma_{C3\text{-}C4}$-$\pi^*_{C=O}$ interactions (6.89 kcal mol^{-1}) is superior by 0.37 kcal mol^{-1} to the sum of $\sigma_{C1\text{-}C6}$-$\pi^*_{C=O}$ and $\sigma_{C4\text{-}C5}$-$\pi^*_{C=O}$ interactions (6.52 kcal mol^{-1}), one is led to predict *anti*-addition. This, however, contrasts the Cieplak model which predicts $\sigma_{C1\text{-}C2}$ and $\sigma_{C3\text{-}C4}$ to be inferior to $\sigma_{C1\text{-}C6}$ and $\sigma_{C4\text{-}C5}$ in their electron-donating abilities due to the *–I* effects of the ester functions. This reversal is due to the orientation effects arising from the ester functions that allow $\pi_{C=O}$-$\sigma^*_{C1\text{-}C2}$ (1.59 kcal mol^{-1} on C2) and $\sigma_{C\text{-}O}$-$\sigma^*_{C3\text{-}C4}$ (1.42 kcal mol^{-1} on C3) interactions. These relative electron-donating abilities were reconfirmed in **19f**-H^+ in which C7-ketone was protonated; the sum of

$\sigma_{C1\text{-}C2}$-$\pi^*_{C=O}$ and $\sigma_{C3\text{-}C4}$-$\pi^*_{C=O}$ interactions (14.23 kcal mol^{-1}) was better than the sum of $\sigma_{C1\text{-}C6}$-$\pi^*_{C=O}$ and $\sigma_{C4\text{-}C5}$-$\pi^*_{C=O}$ interactions (13.78 kcal mol^{-1}). The *app*-effects, therefore, predicted *anti*-addition, which is in clear violation of the experimental selectivities that varied from 77:23 to 90:10 in favor of *syn*-addition in the reactions with various nucleophiles.

The above discrepancy is not without a good reason. Why must only the 7-keto oxygen undergo cation complexation when the carbonyl oxygen bears a similar or even better charge? The NBO analysis indicated the carbonyl oxygen on C2 to be the most negative of all the oxygen atoms and more negative (0.61 units) than the oxygen of the C7-keto group (0.51 units). This also necessitates cation complexation of the ester oxygen. Both the D1 and D2 and D3 and D4 differences in **19f**-$2H^+$ are now unambiguously in favor of the *syn*-addition, supported by the *app*-effects. The sum of the $\sigma_{C1\text{-}C2}$-$\pi^*_{C=O}$ and $\sigma_{C3\text{-}C4}$-$\pi^*_{C=O}$ interactions (10.51 kcal mol^{-1}) is inferior to the sum of $\sigma_{C1\text{-}C6}$-$\pi^*_{C=O}$ and $\sigma_{C4\text{-}C5}$-$\pi^*_{C=O}$ interactions (14.49 kcal mol^{-1}). A similar conclusion is drawn from the **19f**-$2Li^+$ variant of **19f**-$2H^+$

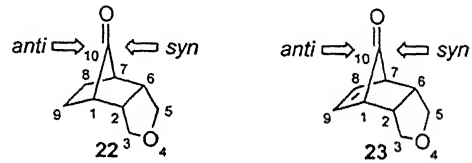


Figure 14. Structures of species **22** and **23**

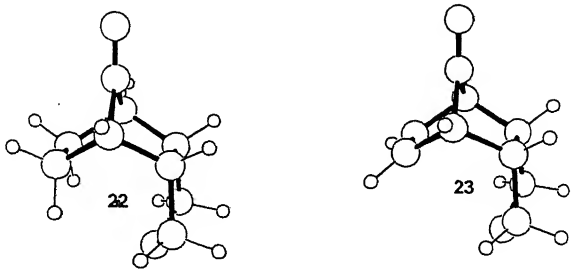
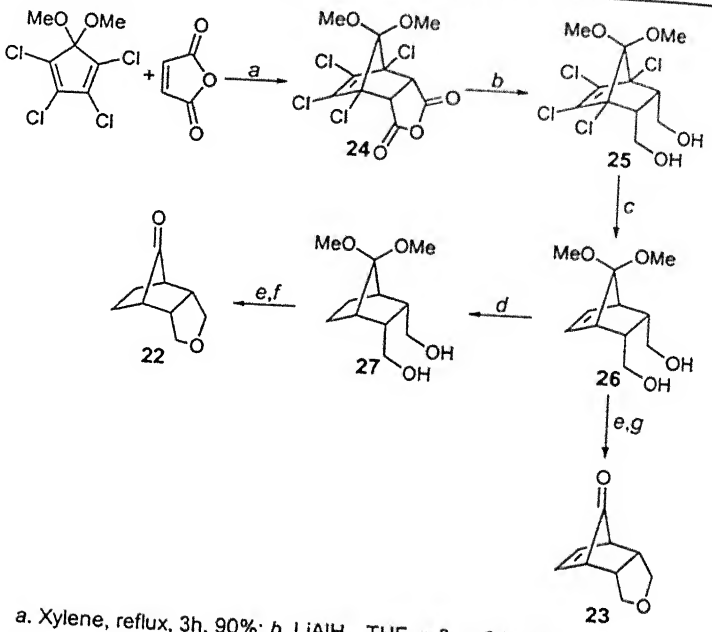


Figure 15. 3D structures of the species **22** and **23**

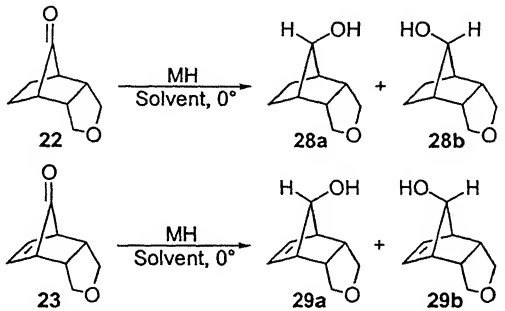
To evaluate the rigid conformer concept in detail, we chose to study 4-oxa-tricyclo[5.2.1.$0^{2,6}$]decan-10-one, **22** (Figure 14), wherein the ring oxygen is held in such a rigid conformation (Figure 15) that it, indeed, raises the possibility of through-space electron-donation from one of its electron pair orbitals to C1-C2/C6-C7 bonds that, in turn, will favor *anti*-selection. Alternatively, the electron-withdrawing ring oxygen will be expected to reduce the residual charges on C2 and C6 to promote *syn*-selection in compliance with the electrostatic model. Only the reduction of **22** with $NaBH_4$ has been reported and was found to be 1:1.[16a] This led us to study the experimental selectivities with a range of reducing agents. We have also studied 4-oxa-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-one, **23**, to examine the competing effect of the unsaturation to that of the heterocyclic ring. The π-route[23a] predicts, *a priori*, the *syn*-selectivity. The electrostatic repulsion in between the olefin and the nucleophile, both electron-rich, also favors *syn*-addition.[24]



a. Xylene, reflux, 3h, 90%; *b*. $LiAlH_4$, THF, reflux, 3 h, 70%;
c. Na, liq. NH_3, THF, 84%; *d*. Pd/C, H_2, EtOAc, 96%; *e*. TsCl, Py, 0 °C;
f. 5% HCl in THF, 0-25 °C, 30 min; *g*. *p*-TSA, acetone, reflux, 8 h

Scheme 1. Syntheses of the species **22** and **23**

The compounds **22** and **23** were prepared as shown in Scheme 1.[23] The Diels-Alder adduct **24**, obtained from the cycloaddition of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and maleic anhydride,[25] was reduced to **25**.[21] Removal of the Cl atoms, leading to **26**, followed by catalytic reduction of the olefinic bond, [21] closure of the heterocyclic ring,[26] and hydrolysis of the acetal function, in that order, furnished **22**. Likewise, closure of the heterocyclic ring in **26** and hydrolysis of the acetal function furnished **23**.



Scheme 2. Reduction of **22** and **23**

Table 3. π-Selectivities of hydride addition to **22** and **23**

Entry	22/23	Hydride	Solvent	Time (h)	Yield (%)	*Anti*:*Syn*
1	22	$NaBH_4$	MeOH	0.5	>95	1.0:1.0
2	22	$NaCNBH_3$	MeOH[a]	0.5	>95	2.1:1.0
3	22	$LiAlH_4$	Et_2O	2.0	>80	1.1:1.0
4	22	DIBAL-H	toluene	2.0	>85	2.0:1.0
5	22	DIBAL-H	toluene[b]	0.5	>85	4.8:1.0
6	22	L-Selectride	THF	1.0	>95	1.0:1.5
7	22	L-Selectride	toluene	1.0	>85	1.0:8.0
8	22	L-Selectride	toluene[b]	2.0	>80	1.3:1.0
9	23	$NaBH_4$	MeOH	1.0	>85	23:1.0
10	23	$NaCNBH_3$	MeOH[a]	1.0	>95	25:1.0
11	23	$LiAlH_4$	Et_2O	2.0	>95	4.5:1.0
12	23	DIBAL-H	toluene	2.0	>75	1.8:1.0
13	23	DIBAL-H	toluene[b]	0.5	>85	>20:1.0
14	23	L-Selectride	THF	1.0	>85	15:1.0
15	23	L-Selectride	toluene	1.0	>85	2.3:1.0

[a] reaction was carried out at pH 3-4; [b] reaction was carried out in the presence of 3 equiv of $TiCl_4$

The stereostructures of the alcohols **28a** and **28b** (Scheme 2) were assigned on the basis of relatively greater deshielding of the C2 and C6 *exo*-protons in **28a**. Similarly, the stereostructures of the alcohols **29a** and **29b** were assigned based on the comparatively higher

deshielding of the C2 and C6 *exo*-protons in the *Z*-alcohol **29a** and the C8 and C9 olefinic protons in **29b**.

The selectivities of **22** and **23** with selected hydrides are collected in Table 3. There is a strong dependence of the selectivity on the specific hydride used and the reaction solvent employed. The selectivity has even reversed, as shown, with the use of L-selectride for the reaction of **22**. Unlike most other reducing agents that favored *anti*-addition, L-selectride favored *syn*-addition. The effect of solvent on the reaction with L-selectride is phenomenal; the selectivity changed from 1:1.5 in THF to 1:8 in toluene (entries 6/7).

The species **23** exhibited *anti*-selectivity throughout. The magnitude of the selectivity was, once again, highly dependent on the source of the hydride used and the solvent employed. Lewis acids promoted *anti*-addition to both **22** and **23**. The exclusive *anti*-addition of DIBAL-H to **23** in the presence of 3 equiv of $TiCl_4$ in toluene (entry 13) is, indeed, remarkable when compared to the only 1.8:1.0 selectivity observed otherwise (entry 12). Throughout, there was no reversal in the selectivity of **23**. This is in contrast with the results for **22** and this demonstrates the dominant role of the π-bond in **23** in guiding nucleophiles to the carbonyl function *syn* to it. Coordination of the π-bond to the nucleophile through a cation and, thus, delivery of the nucleophile to the carbonyl function from *syn* to the π-bond is a distinct possibility. The saturation of the π-bond in the products formed from **23** generated the same species as those obtained from the reaction of **22**.

C2/C6 and C8/C9 in **22** and **23** carry NBO charges of –0.29 and –0.47 and –0.28 and –0.22 *au*, respectively.[27,28] These charges predict, respectively, *syn*- and *anti*-additions to **22** and **23** in accordance with the Houk's electrostatic model. Whereas the charge difference in **23** is too small to explain its high *anti*-selectivity, the weak *anti*-selectivity of **22** observed with the commonly used hydride reagents such as $NaCNBH_3$ and $LiAlH_4$ is clearly against the model. $LiAlH_4$ is often used as a standard nucleophile to probe π-selectivities.

Second Order Perturbation Theory Analysis of Fock Matrix in NBO Basis[29] showed the absence of any through-space electron-donation from the ring-oxygen to $\sigma^*_{C1\text{-}C2}$ and $\sigma^*_{C6\text{-}C7}$ in **22** and **23**. Clearly, an interpretation of the *anti*-selectivities of **22** and **23** based on through-space electron-donation from the substituent oxygen will be faulty. The prominent through-space interactions relevant to the π-selectivities of **22** and **23** are listed in Table 4. The sum of the interactions of $\sigma_{C1\text{-}C2}$ and $\sigma_{C6\text{-}C7}$ with $\pi^*_{C=O}$ is superior to the sum of the interactions of $\sigma_{C1\text{-}C9}$ and $\sigma_{C7\text{-}C8}$ with $\pi^*_{C=O}$ in both the species.

Table 4. Through-space interactions relevant to the π-selectivities of **22** and **23**

Interaction	**22**	**23**	Interaction	**22**	**23**
$\sigma_{C1\text{-}C2}$-$\pi^*_{C=O}$	3.32	3.51	$\sigma_{C7\text{-}C8}$-$\pi^*_{C=O}$	3.19	2.76
$\sigma_{C1\text{-}C9}$-$\pi^*_{C=O}$	3.19	2.76	$\sigma_{C3\text{-}H}$-$\sigma^*_{C1\text{-}C2}$	2.94	2.83
$\sigma_{C6\text{-}C7}$-$\pi^*_{C=O}$	3.32	3.51	$\sigma_{C5\text{-}H}$-$\sigma^*_{C6\text{-}C7}$	2.94	2.83

Let us now understand why $\sigma_{C1\text{-}C2}$-$\pi^*_{C=O}$ and $\sigma_{C6\text{-}C7}$-$\pi^*_{C=O}$ interactions are superior to $\sigma_{C1\text{-}C9}$-$\pi^*_{C=O}$ and $\sigma_{C7\text{-}C8}$-$\pi^*_{C=O}$ interactions.

The carbon-carbon bonds on C2 and C6 are less electron donating than the C-H bonds on C8 and C9. The carbon-carbon bonds on C2 and C6 are rendered further less electron donating because they are substituted by an electron-attracting oxygen atom. The geometrical feature of the heterocyclic ring in **22** and **23** (Figure 14) is such that a C-H bond on C3 and C5 is near antiperiplanar to $\sigma_{C1\text{-}C2}$ and $\sigma_{C6\text{-}C7}$ bonds. This allows for $\sigma_{C3\text{-}H}$-$\sigma^*_{C1\text{-}C2}$ and $\sigma_{C5\text{-}H}$-$\sigma^*_{C6\text{-}C7}$ interactions that are, respectively, 2.94 kcal mol^{-1} and 2.83 kcal mol^{-1} strong in **22** and **23**. These interactions are responsible in enhancing the overall electron donating abilities of $\sigma_{C1\text{-}C2}$ and $\sigma_{C6\text{-}C7}$ to $\pi^*_{C=O}$ that, in turn, support the generally observed *anti*-selectivities.

3.3 Conclusions

While the rigid conformer concept for **19d** is valid in explaining its *anti*-selectivity, it is not so for **19c**. In **19c**, it is rather the electron-donating interaction of one of the two methylene C-H bonds with $\sigma^*_{C1\text{-}C2}$ that plays the key role in promoting the *anti*-pyramidalization. This draws support from the studies on **22** and **23** wherein the ring oxygen is held in a rigid conformation. The π-route argument and the argument of electrostatic repulsion between a π-bond and a nucleophile are invalid to **23**. The experimental selectivities of both **22** and **23** are rather controlled by the antiperiplanar effects that render $\sigma_{C1\text{-}C2}$ and $\sigma_{C6\text{-}C7}$ more electron-rich than $\sigma_{C1\text{-}C9}$ and $\sigma_{C7\text{-}C8}$ by electron-donation from a C-H bond on C3 and C5.

3.4 Experimental

1,2,3,4-Tetrachloro-5,5-dimethoxycyclopentadiene and $Cu(OTf)_2$ were purchased from Aldrich and used as procured. Theoretical calculations were performed on a Silicon Graphics Origin200 computer.

24.[25] A mixture of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (2.77 g, 10.5 mmol) and maleic anhydride (0.981 g, 10 mmol) in dry xylene (15 mL) was refluxed for 3 h under N_2 atmosphere. The reaction mixture, when cooled to 25 °C and filtered, furnished the desired product in crystalline form, 3.62 g, 90%.

25.[21a] To a suspension of $LiAlH_4$ (0.95 g, 25 mmol) in dry THF (10 mL) at 0 °C, a solution of **24** (2.75 g, 7.6 mmol) in THF (15 mL) was added slowly. The reaction mixture was allowed to warm to rt and refluxed for 10 h. The reaction mixture was cooled to 0 °C and quenched with enough EtOAc and water to destroy the excess of $LiAlH_4$. This was filtered and dried. The evaporation of the solvent furnished the crude product that was filtered through a short silica gel column to obtain **25**, 1.87 g, 70%.

26.[21a] A solution of **25** (1.29 g, 3.7 mmol) in dry THF (20 mL) was added to liquid NH_3 (300 mL) in a 500 mL 2 necked round bottom flask fitted with a KOH guard tube and a rubber septum and cooled to – 80 °C. To this, small Na pieces were added until the permanent blue color appeared. The NH_3 was allowed to evaporate to leave behind a residue to which saturated aq NH_4Cl (40 mL) was added. This was extracted with EtOAc (3 x 15 mL) and the extract washed with brine and dried.

The removal of solvent furnished a residue that was purified by silica gel column chromatography to obtain the desired product, 0.66 g, 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08-6.06 (2H, m), 4.25-4.05 (2H, br s), 3.60-3.56 (2H, dd, J = 11.1, 3.5 Hz), 3.46 (2H, t, J = 10.5 Hz), 3.24 (3H, s), 3.12 (3H, s), 2.87-2.83 (2H, m), 2.73 (2H, br d, J = 6.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 118.2, 62.1, 51.7, 49.7, 48.6, 42.7. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.65; H, 8.47. Found: C, 61.48; H, 8.34.

23.[26] *p*-TsCl (0.321 g, 1.68 mmol) was added in portions over 1 h to a solution of **26** (0.360 g, 1.68 mmol) in pyridine (4 mL) at 0 °C. The reaction mixture was warmed to rt and refluxed for 5 h. The mixture was poured into water (10 mL) and extracted with chloroform (4 x 5 mL). The combined extracts were washed with water (1 x 6 mL) and 5% aq HCl (2 x 6 mL). Drying and solvent removal furnished a residue, 0.235 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24-6.22 (2H, m), 3.66-3.61 (2H, m), 3.49-3.46 (2H, dd, J = 9.0, 2.9 Hz), 3.22 (3H, s), 3.14 (3H, s), 3.04-3.01 (2H, m), 2.95-2.92 (2H, quintet, J = 2.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 122.2, 69.3, 51.9, 49.8, 48.0, 45.1. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.31; H, 8.22. Found: C, 67.20; H, 8.10.

A solution of the above crude material and two crystals of *p*-TSA in acetone (10 mL) was refluxed for 8 h. The solvent was removed and the residue chromatographed over silica gel to obtain **23**, 0.080 g, 31%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50-6.48 (2H, m), 3.83-3.79 (2H, m), 3.54 (2H, br d, J = 9.2 Hz), 3.14-3.09 (2H, m), 3.04-2.97 (2H, m). ^{13}C (100 MHz, $CDCl_3$) δ 201.4, 131,0, 70.4, 50.3, 41.6. Anal. Calcd for $C_9H_{10}O_2$: C, 71.97; H, 6.72. Found: C, 72.02; H, 6.60.

27.[21a] To a solution of **26** (0.660 g, 3.08 mmol) in EtOAc (10 mL), 5% Pd/C (0.010 g) was added. The flask was evacuated at a water aspirator and the vacuum released in a balloon filled with H_2. The resultant solution was stirred at 25 °C under H_2 atmosphere for 12 h. It was filtered through a short pad of celite and concentrated on a rotovap. The residue was chromatographed over silica gel to furnish **27**, 0.640 g, 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65-4.15 (2H, br s), 4.03-3.94 (2H, m), 3.59 (2H, d, J = 11.0 Hz), 3.3.0 (3H, s), 3.25 (3H,s), 2.55-2.40 (2H, m), 2.12-2.04 (2H, m), 1.63-1.53 (2H, m), 1.37 (2H, d, J = 8.1 Hz). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.07; H, 9.33. Found: C, 60.90; H, 9.22.

22.[26] To a solution of **27** (0.200 g, 0.926 mmol) in dry pyridine (2 mL), *p*-TsCl (0.177 g, 0.926 mmol) was added in portions over a period of 1 h at 0 °C. After stirring for 4 h at 25 °C, the reaction mixture was poured into water (10 mL) and extracted with chloroform (4 x 5 mL). The combined extracts were washed with water (1 x 7 mL), 5% aq HCl (1 x 7 mL), and brine (1 x 7 mL). The solvent was removed to obtain a residue, 0.152 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (2H, d, J = 9.8 Hz), 3.46-3.42 (2H, m), 3.29 (3H, s), 3.28 (3H, s), 2.76-2.71 (2H, m), 2.08-2.03 (2H, m), 1.58-1.56 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.5, 68.6, 50.5, 42.8, 41.4, 20.8. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.16. Found: C, 66.50; H, 9.02.

The above residue was dissolved in 5% HCl in THF (5 mL) and stirred for 30 min at 25 °C. The reaction mixture was diluted with Et_2O (20 mL) and washed with water (2 x 10 mL) and brine (1 x

mL). Drying and solvent removal furnished a residue that was chromatographed over silica gel to obtain **22**, 0.062 g, 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (1H, d, J = 10.2 Hz), 3.61-3.57 (1H, m), 2.77-2.69 (1H, m), 2.06-1.99 (1H, m), 1.90-1.86 (1H, m), 1.71-1.57 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 68.9, 42.4, 37.6, 171. Anal. Calcd for $C_9H_{12}O_2$: C, 71.01; H, 7.95. Found: C, 70.90; H, 7.82.

Typical Procedure for Reduction with $NaBH_4$. $NaBH_4$ (0.2 mmol) was added to a solution of the substrate (0.2 mmol) in MeOH (2 mL) at 0 °C. After the reaction mixture was stirred for the specified time given in Table 1, MeOH was removed. Saturated aq NH_4Cl (2 mL) was added to the residue and the product(s) extracted into EtOAc (2 x 5 mL). The combined EtOAc solution was dried and the EtOAc evaporated. The residue, thus left, was filtered through a small column of silica gel to furnish a mixture of the desired alcohols.

Typical Procedure for Reduction with $Na(CN)BH_3$. A small crystal of methyl orange was added to a solution of the substrate (0.2 mmol) in MeOH (2 mL) at 0 °C. The solution turned yellow. Drops of 2N HCl/MeOH were added so that the solution turned red. Now, $Na(CN)BH_3$ (0.2 mmol) was added slowly. Whenever the color of the reaction mixture started to turn to yellow during the addition of $Na(CN)BH_3$, drops of 2N HCl/MeOH were added immediately to restore the red color. When the reaction was complete, it was concentrated on a rotovap under reduced pressure. Saturated aq NH_4Cl (2 mL) was added to the residue and the product(s)

EtOAc evaporated. The residue, thus left, was filtered through a small column of silica gel to furnish a mixture of the desired alcohols.

Typical Procedure for Reduction with $LiAlH_4$. $LiAlH_4$ (0.2 mmol) was added to a stirred solution of the substrate (0.2 mmol) in anhydrous Et_2O (2 mL) at 0 °C. After the reaction mixture was stirred for the specified time given in Table 1 at the same temperature, enough EtOAc (2 mL) and water (2 drops) were added to destroy the excess $LiAlH_4$. Saturated aq NH_4Cl (2 mL) was added to the residue and the product(s) extracted into EtOAc (2 x 5 mL). This was filtered and the organic solution dried. The evaporation of the solvents and filtration of the residue, thus obtained, through a short column of silica gel furnished a mixture of the desired alcohols.

Typical Procedure for Reduction with L-Selectride. A 1M solution of L-Selectride in THF (0.3 mL, 0.3 mmol) was added to a magnetically stirred solution of the substrate (0.2 mmol) in the solvent (1.7 mL) of choice at 0 °C. The stirring was continued at this temperature until the reaction was complete. MeOH (0.2 mL), 1N NaOH (0.2 mL), and 30% H_2O_2 (0.2 mL) were added and the reaction mixture allowed to warm up to rt and stirred for 30 min. Extraction with EtOAc (2 x 5 mL) followed by washing with brine, drying, and evaporation furnished a residue which was filtered through a short column of silica gel to furnish a mixture of the desired alcohols.

Typical Procedure for Reduction with DIBAL-H. A 1M solution of DIBAL-H in toluene (0.3 mL, 0.3 mmol) was added to a stirred solution of the substrate (0.2 mmol) in anhydrous toluene (1.7 mL) at 0

°C. The stirring at 0 °C was continued until the reaction was complete. The reaction was quenched with 5% aq HCl (2 mL) and extracted with EtOAc (2 x 5 mL). The combined extract was washed with water (1 x 3 mL) and brine (1 x 3 mL). The residue obtained after solvent removal was filtered through a short column of silica gel to furnish a mixture of the desired alcohols.

General Procedure for the Reduction in the presence of $TiCl_4$. $TiCl_4$ (0.6 mmol) was added slowly to a solution of the substrate (0.2 mmol) in a solvent (1.7 mL) at 0 °C. This was stirred at 0 °C for 15 min and then the hydride reagent (0.3 mmol) was added. After the reaction was complete, it was quenched with 5% aq HCl (2 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine and dried. The crude material obtained from solvent evaporation was filtered through a silica gel column to furnish the desired alcohols.

28a. Characteristic peaks in the ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.32 (1H, s), 3.93 (2H, d, J = 9.8 Hz), 3.53-3.49 (2H, m), 2.92-2.88 (2H, m), 2.02-1.97 (2H, m).

28b. Characteristic peaks in the ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (1H, s), 3.92 (2H, d, J = 10.0 Hz), 3.39-3.35 (2H, m), 2.51-2.48 (2H, m), 2.08-2.04 (2H, m).

29a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (2H, t, J = 2.2 Hz), 3.80 (1H, s), 3.70-3.63 (2H, m), 3.59-3.57 (2H, dd, J = 8.8, 2.2 Hz), 3.13-3.08 (2H, m), 2.71-2.68 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.4, 87.7, 69.3, 50.0, 45.2.

29b. Characteristic peaks in the ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24-6.22 (2H, m), 3.91 (1H, s), 3.45-3.42 (2H, dd, J = 8.9, 2.8 Hz), 2.94-2.92 (2H, m), 2.86-2.83 (2H, m).

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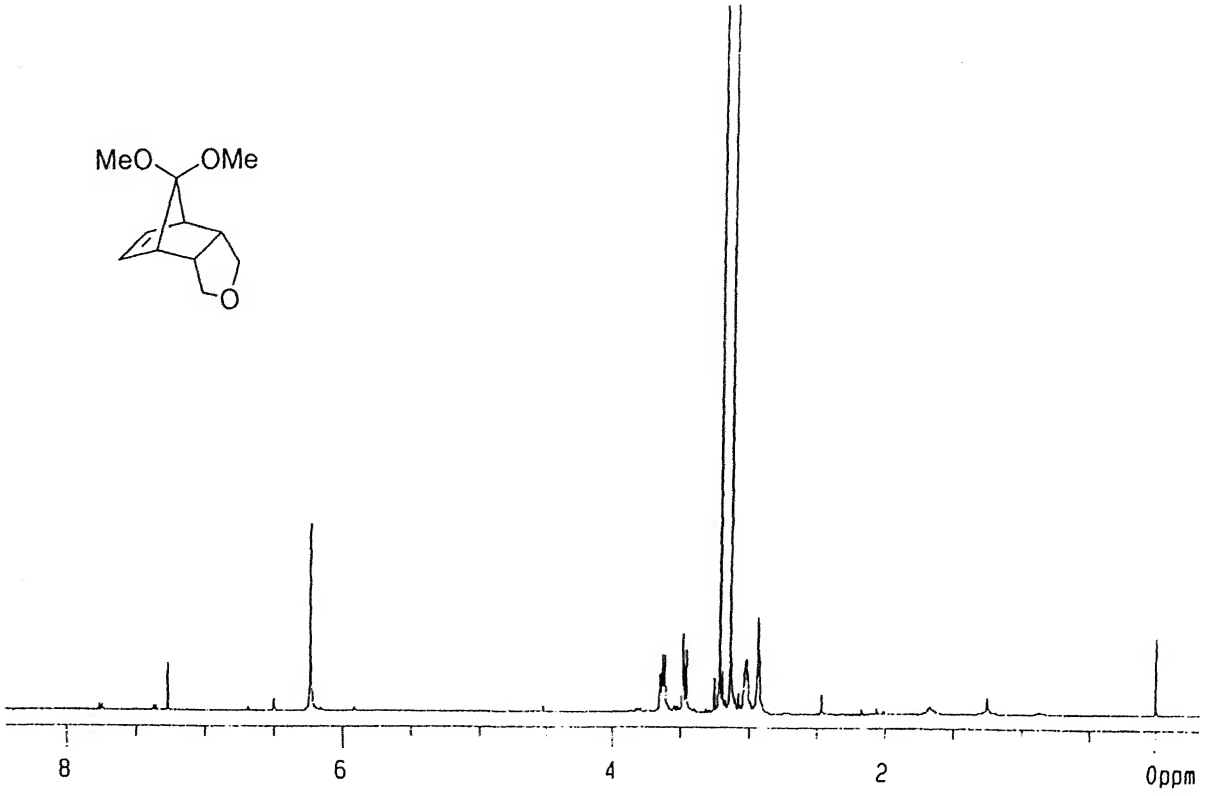

Figure 16. 400 MHz ^{1}H NMR spectrum of dimethyl ketal of **23**

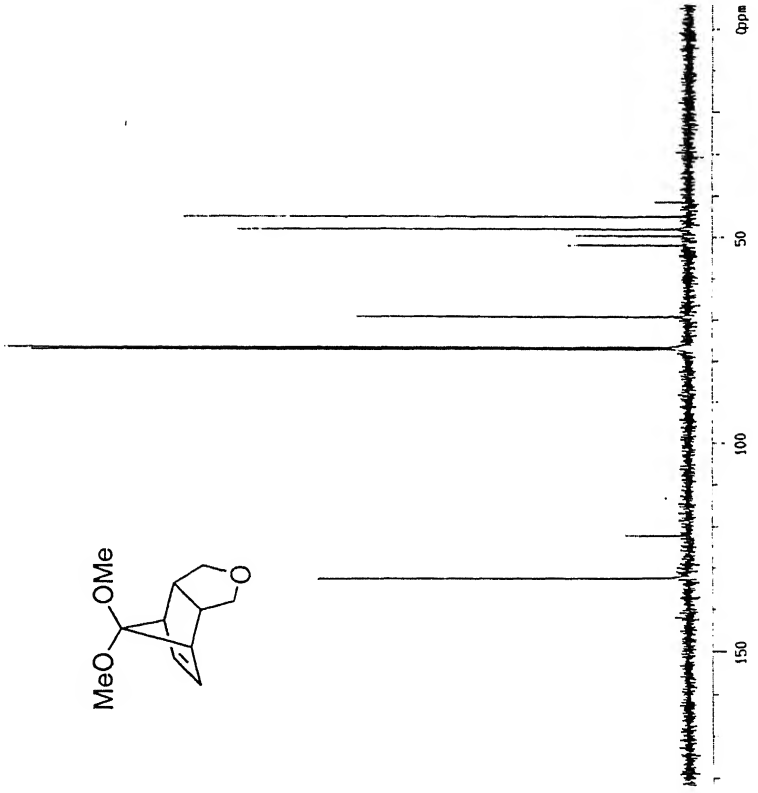

Figure 17. 100 MHz ^{13}C NMR spectrum of dimethyl ketal of **23**

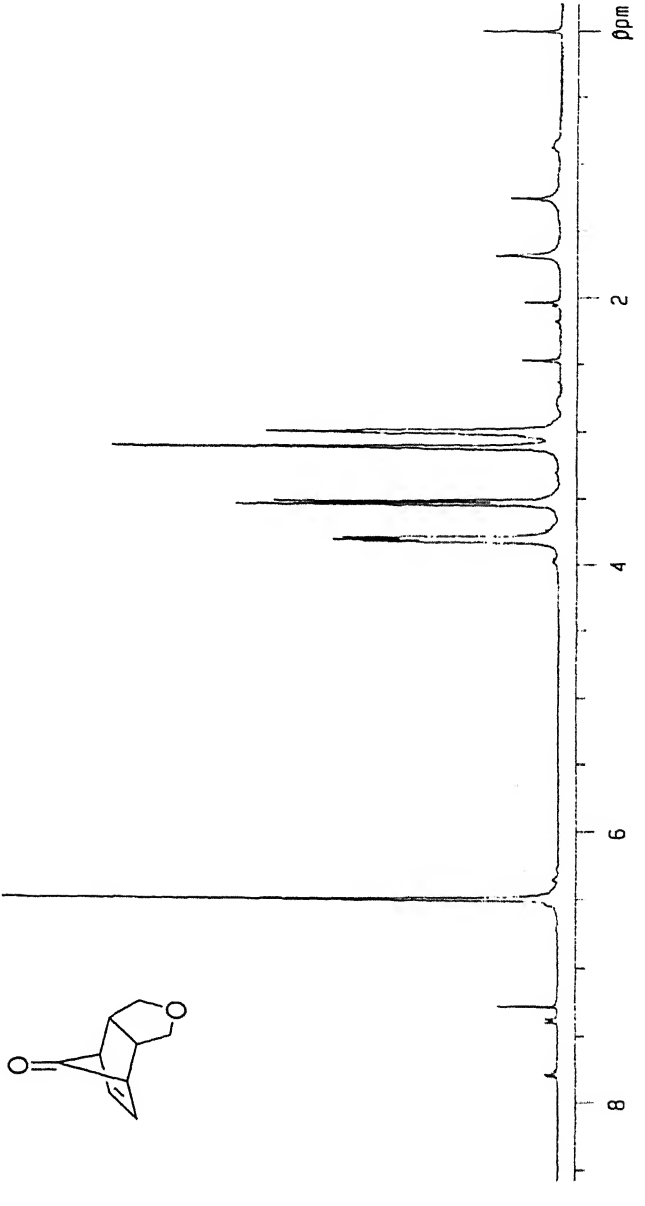

Figure 18. 400 MHz ^{1}H NMR spectrum of **23**

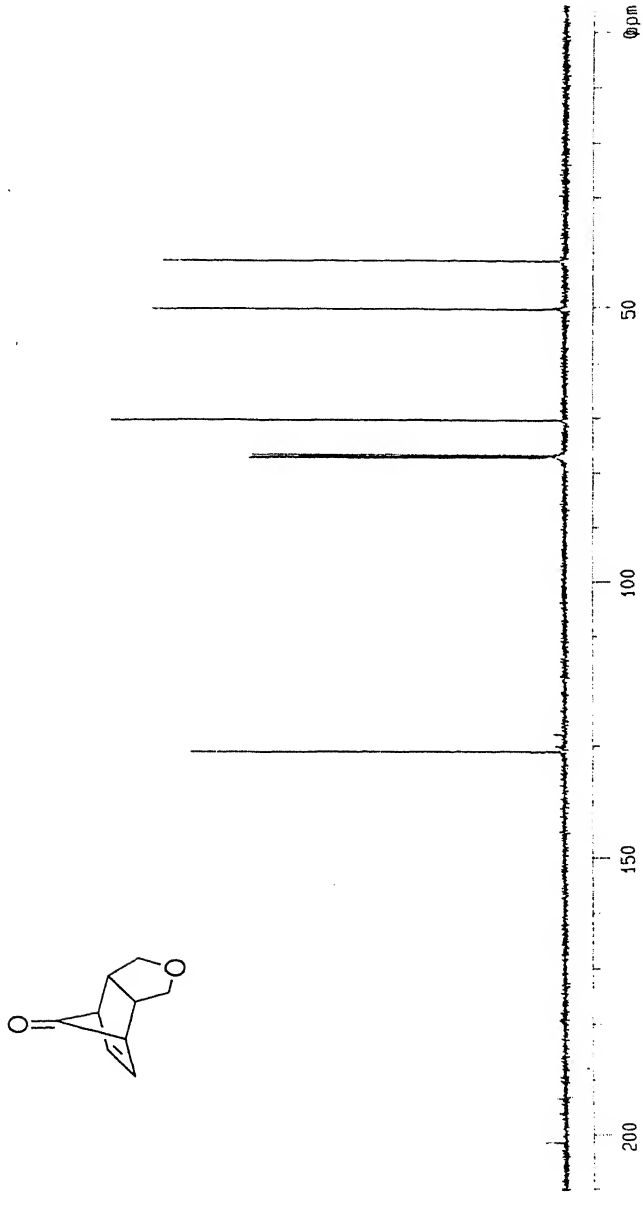

Figure 19. 100 MHz ^{13}C NMR spectrum of **23**

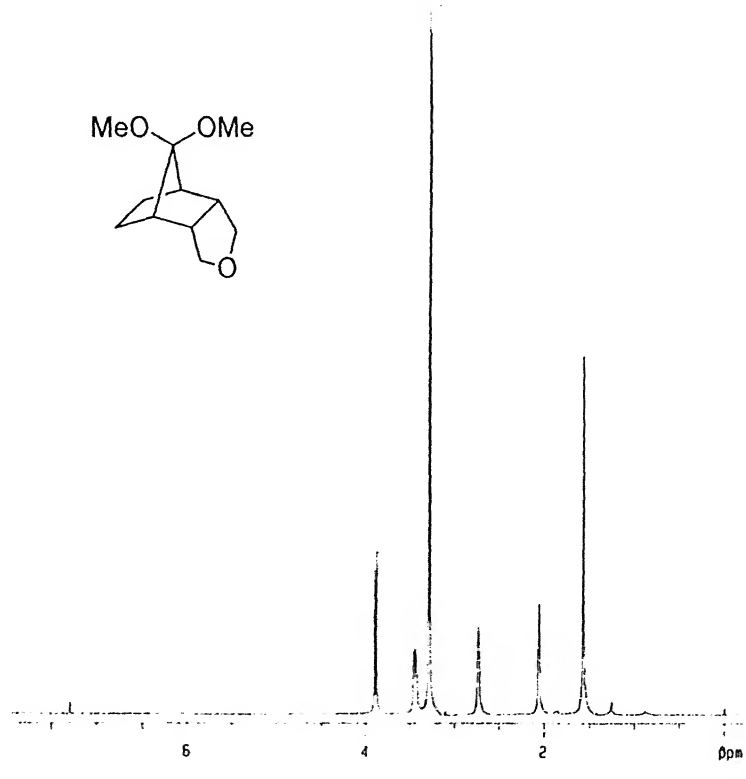

Figure 20. 400 MHz ^{1}H NMR spectrum of dimethyl ketal of **22**

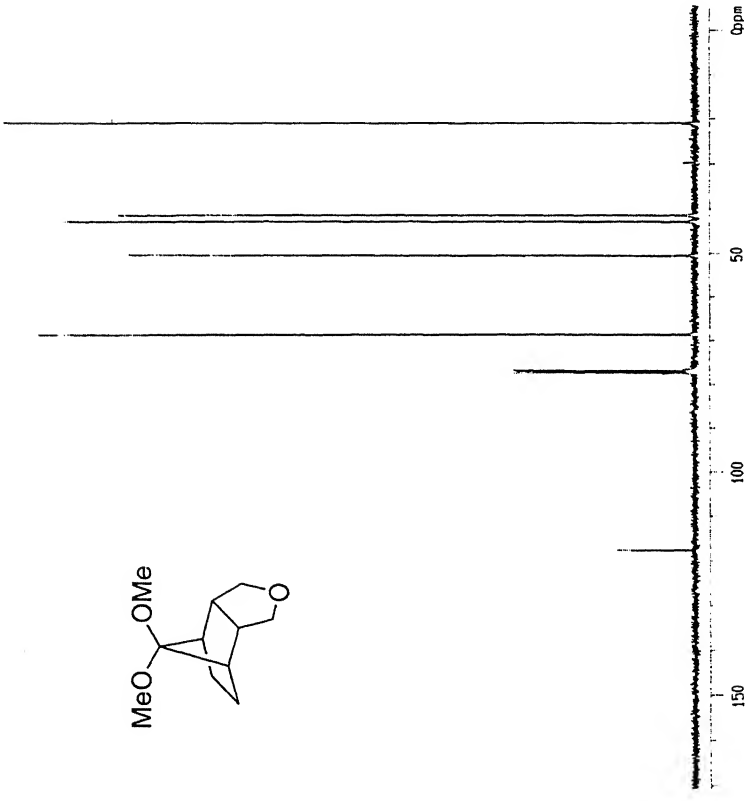

Figure 21. 100 MHz ^{13}C NMR spectrum of dimethyl ketal of **22**

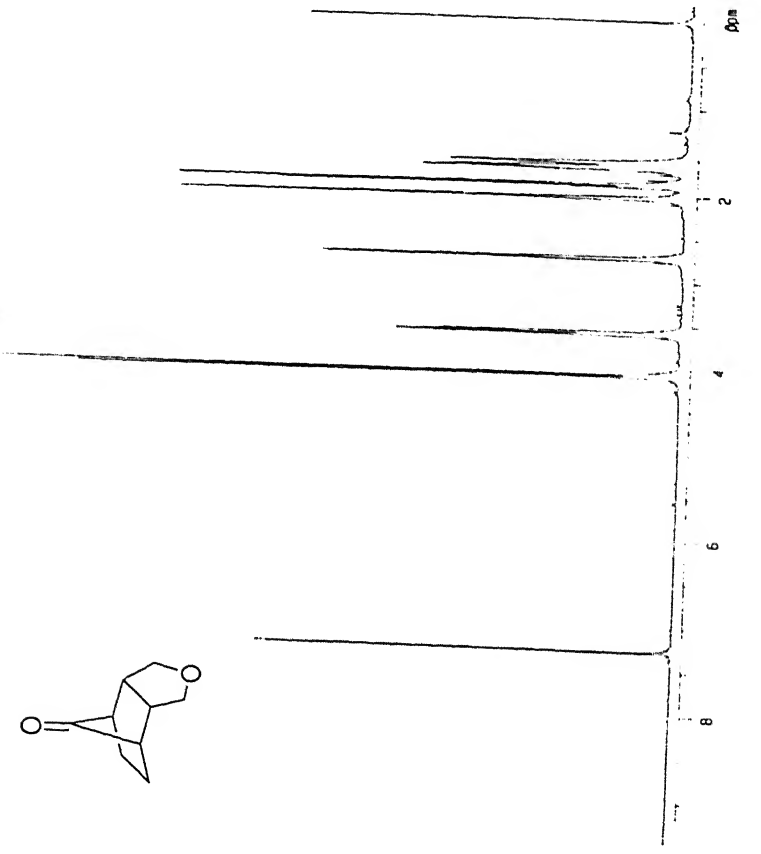

Figure 22. 400 MHz ^{1}H NMR spectrum of **22**

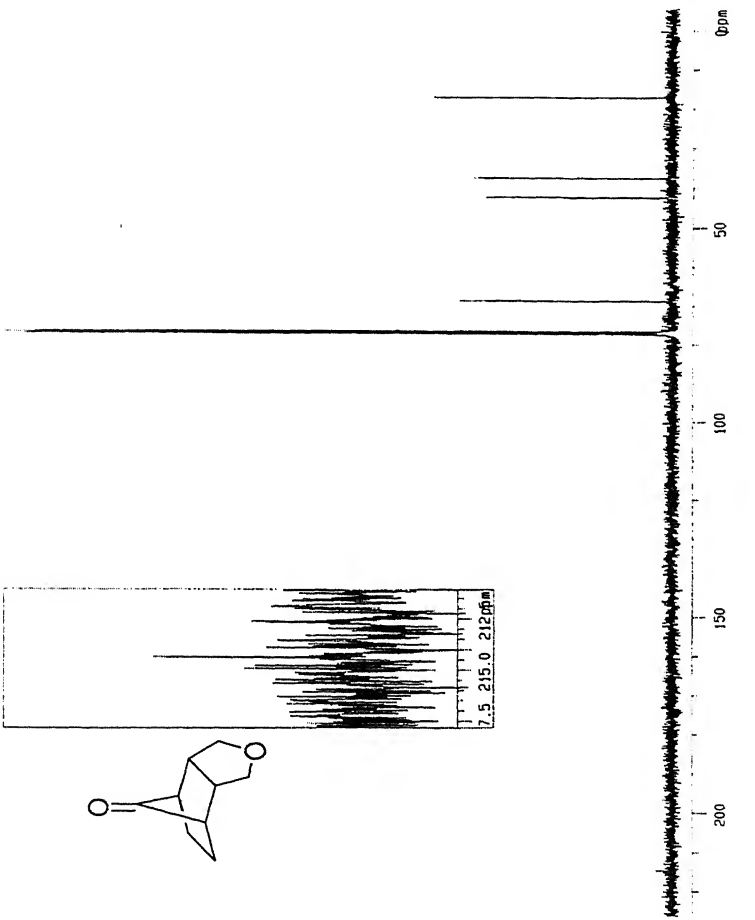

Figure 23. 100 MHz ^{13}C NMR spectrum of **22**

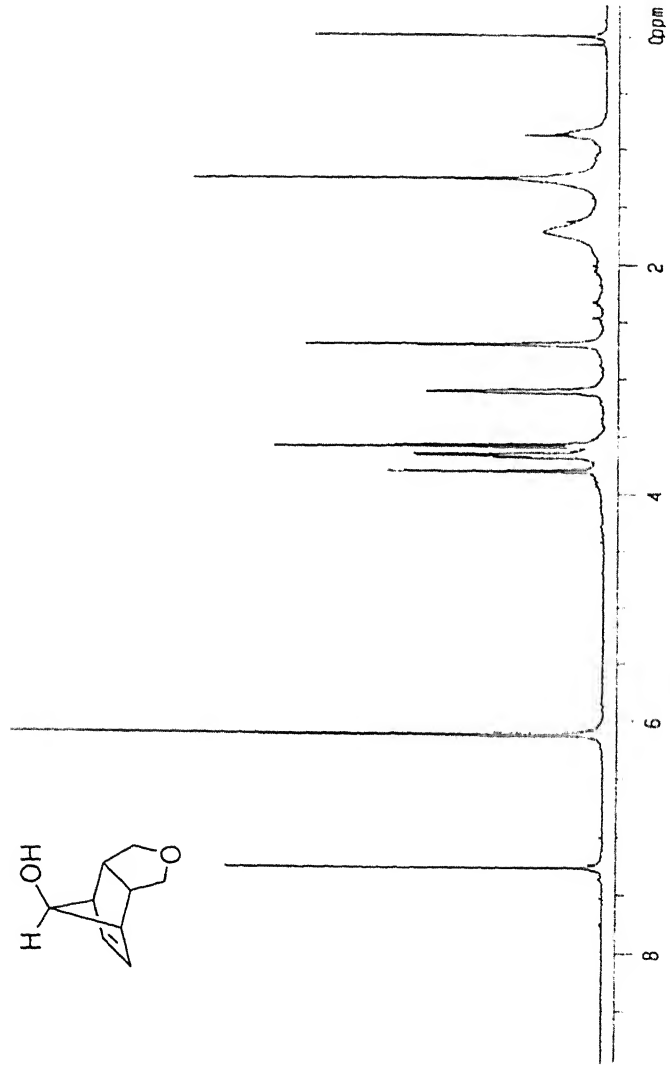

Figure 24. 400 MHz ^{1}H NMR spectrum of **29a**

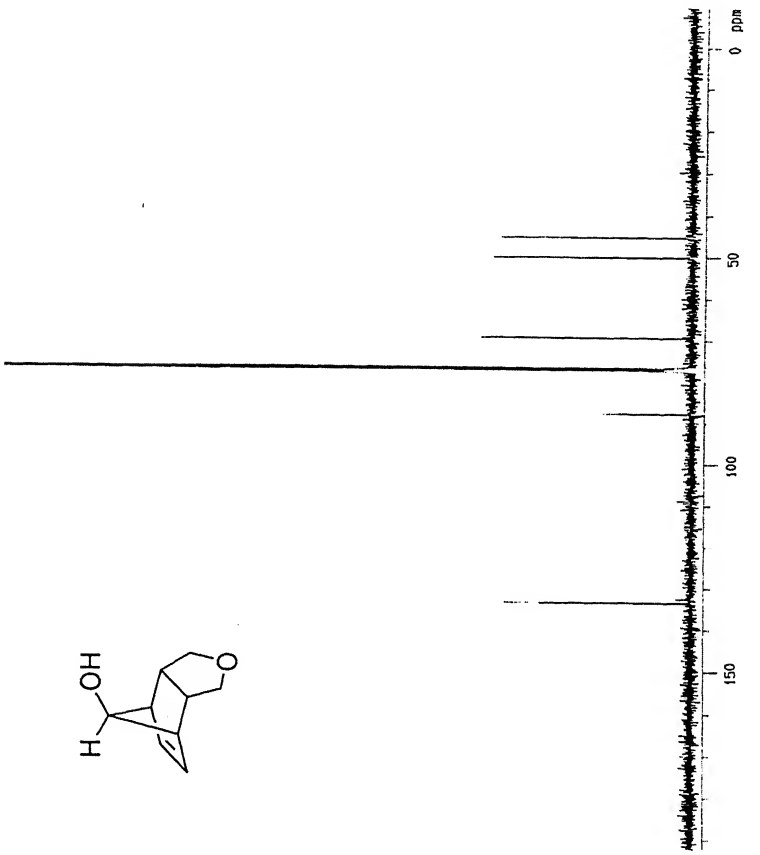

Figure 25. 100 MHz ^{13}C NMR spectrum of **29a**

List of Publications

1. Silicon-Assisted Ring Opening of Donor-Acceptor Substituted Cyclopropanes. An Expedient Entry to Substituted Dihydrofurans

   Veejendra K. Yadav* and Rengarajan Balamurugan

   Org. Lett. **2001**, *3*, 2717.

2. Synthesis of γ-Methylene Oxacycles and α- and β-Alkylidene Lactones *via* Silicon-Assisted Ring Opening of Cyclopropyl Carbinols

   Veejendra K. Yadav* and Rengarajan Balamurugan

   Chem. Commun. **2002**, 514.

3. The Thionophosphate-Thiolophosphate Photoisomerization Proceeds Predominantly Through a Non-Chain Pathway. Synthetically Viable Benzylation of Tetrahydrofuran, Propan-2-ol, and Olefins

   Veejendra K. Yadav*, Rengarajan Balamurugan, Masood Parvez and Raghav Yamdagni

   J. Chem. Soc., Perkin Trans 1. **2001**, 323.

4. Comparison of the Cieplak Model and the Cation Complexation Model as Applied to Selected 2,3-Disubstituted norbornan-7-ones

   Veejendra K. Yadav* and Rengarajan Balamurugan

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5. 4-Oxa-tricyclo[5.2.1.$0^{2,6}$]decan-10-one and 4-Oxa-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-one. Experimental and DFT Investigations of the π-Selectivities

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   J. Org. Chem. **2002**, *67*, 587.